PCT/EP 03 / 03466

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APPLICATION NUMBER: ***60/369,779***
FILING DATE: ***April 03, 2002***

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

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04 03-02 A/PROV

JC882 U.S. PTO 04/03/02

Docket Number	4-32445P1/PROV/USN

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EL 790909723 US	April 3, 2002
Express Mail Label Number	Date of Deposit

JC996 U.S. PTO 60/369779 04/03/02

Address to: Assistant Commissioner for Patents
Box Provisional Patent Application
Washington, DC 20231

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

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TITLE OF THE INVENTION (280 characters max)

CYCLIC SULFAMIDE DERIVATIVES AND METHODS OF USE

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (Including Any Claims and Abstract) – 120 pages
- ☐ Drawings – sheets
- ☒ Other (specify): Application data sheet

METHOD OF PAYMENT

The Commissioner is hereby authorized to charge filing fee and any additional fees required to Deposit Account Number: 19-0134 in the name of Novartis Corporation.	PROVISIONAL FILING FEE AMOUNT: $ 160

☐ U.S. Government agency and contract number: (if the invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.)

Respectfully submitted,

Date: April 3, 2002

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Correspondence Customer Number:: 001095

APPLICATION INFORMATION

Title Line One:: CYCLIC SULFAMIDE DERIVATIVES AND METHODS
Title Line Two:: OF USE
Formal Drawings?:: No
Application Type:: Provisional
Docket Number:: 4-32445P1/PR
Secrecy Order in Parent Appl.?:: No

REPRESENTATIVE INFORMATION

Representative Customer Number:: 1095

Source:: PrintEFS Version 1.0.1

CYCLIC SULFAMIDE DERIVATIVES AND METHODS OF USE

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to cyclic sulfamide derivatives, more specifically 1,1-dioxo-1,2,5-thiadiazolidine derivatives, pharmaceutical compositions containing them, and to methods of treating conditions associated with protein tyrosine phosphatase (PTPase) activity, in particular, PTPase-1B (PTP-1B) activity.

Description of Related Art

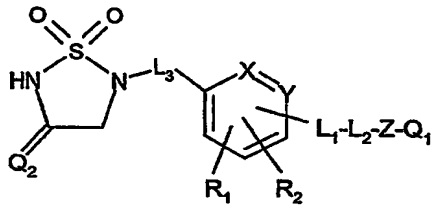
Type 2 (non-insulin-dependent) diabetes mellitus is often associated with an inability of insulin to function properly, referred to as insulin resistance. A current hypothesis for one of the causes of insulin resistance is faulty insulin signal transduction due to overactive PTPases, a large family of transmembrane or intracellular enzymes. The insulin signaling cascade begins with the binding of insulin to it's receptor, which initiates autophosphorylation of insulin receptor tyrosine residues, and terminates with the dephosphorylation of these tyrosine residues by insulin receptor associated PTPase. The enzymes that appear most likely to closely associate with the insulin receptor include intracellular PTP-1B (B. J. Goldstein, *J. Cellular Biochemistry* 1992, 48, 33; B. J. Goldstein, *Receptor* 1993, 3, 1-15; F. Ahmad and B. J. Goldstein, *Biochim. Biophys. Acta* 1995, 1248, 57-69). Inhibitors of insulin receptor associated PTPase may thus reduce insulin resistance by delaying deactivation of the insulin receptor and thereby prolonging insulin receptor signaling and increasing glucose clearance.

The insulin receptor requires autophosphorylation of specific tyrosine residues in the activation loop for activity. Upon binding insulin, the autophosphorylated receptor initiates a series of events resulting in glucose uptake from the blood. The insulin receptor is rapidly inactivated through dephosphorylation of these residues by associated protein tyrosine phosphatase, in particular PTP-1B. By inhibiting the dephosphorylation and prolonging the active state, inhibitors of the insulin receptor-associated PTPase may prolong insulin receptor signalling and enhance uptake of circulating glucose.

Inhibitors of PTP[redacted] have been demonstrated to improve insulin sensitivity in vivo, and PTP-1B inhibitors have also been shown to exhibit a beneficial reduction in triglycerides and lipids.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds of the formula



(I)

wherein

R_1 and R_2 are independently hydrogen, halogen, hydroxy, alkoxy, carboxy, cyano, nitro, trifluoromethyl, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, alkylthio, aralkylthio, arylthio, optionally substituted amino, aralkyl, aralkoxy, aryloxy, heteroaralkyl, heteroaralkoxy or heteroaryloxy; or

C-R_1 is nitrogen or N→O; or

R_1 and R_2 combined together with the carbon atoms to which R_1 and R_2 are attached form an optionally substituted fused 5- to 6-membered aromatic or heteroaromatic ring provided that R_1 and R_2 are attached to carbon atoms adjacent to each other; or

R_2 is $-C(O)R_3$ wherein

R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

L_1 is a single bond; or

L_1 is carbon which combined together with R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is CH or nitrogen which taken together with R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur; or

L_1 is CH, oxygen, sulfur or nitrogen provided L_2 is carbon which combined together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is $-CH_2-$, oxygen, sulfur or $-NR_6-$ provided L_2 is CH which taken together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl; or

L_2 is $-(CHR_7)_n-$ wherein

R_7 is hydrogen, hydroxy, alkoxy, carboxy, optionally substituted alkyl, cycloalkyl, aryl or heteroaryl;

n is zero or an integer from 1 to 4;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, carbamoyl, sulfonyl, acyl or acylamino;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(a) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl provided that Q_1 is not hydrogen when

R_1 and R_2 are hydrogen;

X and Y are CH;

L_1 is a single bond;

L_2 is $-(CHR_7)_n-$ wherein R_7 is hydrogen and n is zero;

Z is $-(CHR_8)_m-$ wherein R_8 is hydrogen and m is zero;

L_3 is $-(CHR_7)_s-$ wherein R_8 is hydrogen and s is 1; and

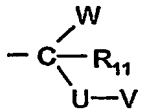
Q_2 is oxygen;

(b) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are as defined for R_3;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

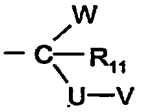
U is $-C(O)-$, $-S(O)_2-$ or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

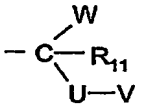
R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero; or

(e) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is $-NR_4R_5$, and R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

L_3 is $-(CHR_7)_s-$ wherein

R_7 is as defined for L_2;

s is an integer from 1 to 3;

Q_2 is oxygen, sulfur or NR_{13} wherein

R_{13} is hydrogen, hydroxy or lower alkyl;

X and Y are independently CH or nitrogen; or

$-X=Y-$ is sulfur, oxygen or $-NR_{14}-$ wherein

R_{14} is hydrogen, optionally substituted alkyl, alkoxycarbonyl, acyl, aryloxycarbonyl, heteroaryloxycarbonyl, carbamoyl or sulfonyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

In another aspect, the present invention provides pharmacological agents which are inhibitors of PTPases, in particular, the compounds of the present invention inhibit PTP-1B, and thus may be employed for the treatment of conditions associated with PTPase activity. The compounds of the present invention may also be employed for inhibition of other enzymes with a phosphotyrosine binding region such as the SH2 domain. Accordingly, the compounds of formula I may be employed for prevention or treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels. The compounds of the present invention may also be employed in the treatment, prevention or control of a number of conditions that accompany Type 2 diabetes, including hyperlipidemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, irritable bowel syndrome, pancreatitis, adipose cell tumors and carcinomas such as liposarcoma, dyslipidemia, and other disorders where insulin resistance is indicated. In addition, the compounds of the present invention may be employed to treat

or prevent cancer, osteoporosis, neurodegenerative and infectious diseases, and diseases involving inflammation and the immune system.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to cyclic sulfamide derivatives, more specifically 1,1-dioxo-1,2,5-thiadiazolidine derivatives, pharmaceutical compositions containing them, methods for preparing the compounds and methods of treating conditions associated with PTPase activity, in particular PTP-1B activity. The compounds of the present invention may also be employed in combination with ligands for other enzymes with a phosphotyrosine binding region such as the SH2 domain.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification unless they are otherwise limited in specific instances either individually or as part of a larger group.

The term "optionally substituted alkyl" refers to unsubstituted or substituted straight or branched chain hydrocarbon groups having 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl and the like. Substituted alkyl groups include, but are not limited to, alkyl groups substituted by one or more of the following groups: halo, hydroxy, cycloalkyl, alkanoyl, alkoxy, alkyloxyalkoxy, alkanoyloxy, amino, alkylamino, dialkylamino, acylamino, carbamoyl, thiol, alkylthio, alkylthiono, sulfonyl, sulfonamido, sulfamoyl, nitro, cyano, carboxy, alkoxycarbonyl, aryl, aralkoxy, guanidino, heterocyclyl including indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl, piperidyl, morpholinyl and the like.

The term "lower alkyl" refers to those alkyl groups as described above having 1 to 7, preferably 1 to 4 carbon atoms.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "alkenyl" refers to any of the above alkyl groups having at least 2 carbon atoms and further containing at least one carbon to carbon double bond. Groups having two to four carbon atoms are preferred.

The term "alkynyl" refers to any of the above alkyl groups having at least two carbon atoms and further containing at least one carbon to carbon triple bond. Groups having two to four carbon atoms are preferred.

The term "alkylene" refers to a straight chain bridge of 1 to 6 carbon atoms connected by single bonds (e.g., $-(CH_2)_x-$ wherein x is 1 to 6), which may be interrupted with one or more heteroatoms selected from oxygen, sulfur and nitrogen, and may be substituted with 1 to 3 substituents such as alkyl, alkoxy, halo, hydroxy, cycloalkyl, alkanoyl, alkyloxyalkoxy, alkanoyloxy, amino, alkylamino, dialkylamino, acylamino, carbamoyl, thiol, alkylthio, alkylthiono, sulfonyl, sulfonamido, sulfamoyl, nitro, cyano, carboxy, alkoxycarbonyl, aryl, aralkoxy, guanidino, heterocyclyl including indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl, piperidyl, morpholinyl and the like.

The term "cycloalkyl" refers to optionally substituted monocyclic, bicyclic or tricyclic hydrocarbon groups of 3 to 12 carbon atoms, each of which may be substituted by one or more substituents such as alkyl, halo, oxo, hydroxy, alkoxy, alkanoyl, acylamino, carbamoyl, alkylamino, dialkylamino, thiol, alkylthio, nitro, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, sulfonyl, sulfonamido, sulfamoyl, heterocyclyl and the like.

Exemplary monocyclic hydrocarbon groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl and the like.

Exemplary bicyclic hydrocarbon groups include bornyl, indyl, hexahydroindyl, tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl and the like.

Exemplary tricyclic hydrocarbon groups include adamantyl and the like.

The term "alkoxy" refers to alkyl-O-.

The term "alkanoyl" refers to alkyl-C(O)-.

The term "alkanoyloxy" refers to alkyl-C(O)-O-.

The terms "alkylamino" and "dialkylamino" refer to alkyl-NH- and $(alkyl)_2N$-, respectively.

The term "alkanoylamino" refers to alkyl-C(O)-NH-.

The term "alkylthio" refers to alkyl-S-.

The term "alkylaminothiocarbonyl" refers to alkyl-NHC(S)-.

The term "trialkylsilyl" refers to $(alkyl)_3Si$-.

The term "trialkylsilyoxy" refers to $(alkyl)_3SiO$-.

The term "alkylthiono" refers to alkyl-S(O)-.

The term "alkylsulfonyl" refers to alkyl-$S(O)_2$-.

The term "alkoxycarbonyl" refers to alkyl-O-C(O)-.

The term "alkoxycarbonyloxy" refers to alkyl-O-C(O)O-.

The term "carboxycarbonyl" refers to HO-C(O)C(O)-.

The term "carbamoyl" refers to $H_2NC(O)$-, alkyl-NHC(O)-, $(alkyl)_2NC(O)$-, aryl-NHC(O)-, alkyl(aryl)-NC(O)-, heteroaryl-NHC(O)-, alkyl(heteroaryl)-NC(O)-, aralkyl-NHC(O)-, alkyl(aralkyl)-NC(O)- and the like.

The term "sulfamoyl" refers to $H_2NS(O)_2$-, alkyl-$NHS(O)_2$-, $(alkyl)_2NS(O)_2$-, aryl-$NHS(O)_2$-, alkyl(aryl)-$NS(O)_2$-, $(aryl)_2NS(O)_2$-, heteroaryl-$NHS(O)_2$-, aralkyl-$NHS(O)_2$-, heteroaralkyl-$NHS(O)_2$- and the like.

The term "sulfonamido" refers to alkyl-$S(O)_2$-NH-, aryl-$S(O)_2$-NH-, aralkyl-$S(O)_2$-NH-, heteroaryl-$S(O)_2$-NH-, heteroaralkyl-$S(O)_2$-NH-, alkyl-$S(O)_2$-N(alkyl)-, aryl-$S(O)_2$-N(alkyl)-, aralkyl-$S(O)_2$-N(alkyl)-, heteroaryl-$S(O)_2$-N(alkyl)-, heteroaralkyl-$S(O)_2$-N(alkyl)- and the like.

The term "sulfonyl" refers to alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl and the like.

The term "optionally substituted amino" refers to a primary or secondary amino group which may optionally be substituted by a substituent such as acyl, sulfonyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, carboxycarbonyl, carbamoyl, alkylaminothiocarbonyl, arylaminothiocarbonyl and the like.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, tetrahydronaphthyl, biphenyl and diphenyl groups, each of which may optionally be substituted by one to four substituents such as alkyl, halo, hydroxy, alkoxy, acyl, alkanoyloxy, optionally substituted amino, thiol, alkylthio, nitro, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, carbamoyl, alkylthiono, sulfonyl, sulfonamido, heterocyclyl and the like.

The term "monocyclic aryl" refers to optionally substituted phenyl as described under aryl.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "aralkanoyl" refers to aralkyl-C(O)-.

The term "aralkylthio" refers to aralkyl-S-.

The term "aralkoxy" refers to an aryl group bonded directly through an alkoxy group.

The term "arylsulfonyl" refers to aryl-$S(O)_2$-.

The term "arylthio" refers to aryl-S-.

The term "aroyl" refers to aryl-C(O)-.

The term "aroylamino" refers to aryl-C(O)-NH-.

The term "aryloxycarbonyl" refers to aryl-O-C(O)-.

The term "heterocyclyl" or "heterocyclo" refers to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4- to 7-membered monocyclic, 7- to 12-membered bicyclic, or 10- to 15-membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The heterocyclic group may be attached at a heteroatom or a carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, 1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl and the like.

Exemplary bicyclic heterocyclic groups include indolyl, dihydroidolyl, benzothiazolyl, benzoxazinyl, benzoxazolyl, benzothienyl, benzothiazinyl, quinuclidinyl, quinolinyl, tetrahydroquinolinyl, decahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, decahydroisoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]-pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, 1,3-dioxo-1,3-dihydroisoindol-2-yl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), phthalazinyl and the like.

Exemplary tricyclic heterocyclic groups include carbazolyl, dibenzoazepinyl, dithienoazepinyl, benzindolyl, phenanthrolinyl, acridinyl, phenanthridinyl, phenoxazinyl, phenothiazinyl, xanthenyl, carbolinyl and the like.

The term "heterocyclyl" includes substituted heterocyclic groups. Substituted heterocyclic groups refer to heterocyclic groups substituted with 1, 2 or 3 of the following:

(a) alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;
(d) oxo (i.e. = O);
(e) optionally substituted amino, alkylamino or dialkylamino;
(f) alkoxy;
(g) cycloalkyl;
(h) carboxy;
(i) heterocyclooxy;
(j) alkoxycarbonyl, such as unsubstituted lower alkoxycarbonyl;
(k) mercapto;
(l) nitro;
(m) cyano;
(n) sulfamoyl or sulfonamido;
(o) aryl;
(p) alkylcarbonyloxy;
(q) arylcarbonyloxy;
(r) arylthio;
(s) aryloxy;
(t) alkylthio;
(u) formyl;
(v) carbamoyl;
(w) aralkyl; or
(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, acylamino, alkylamino, dialkylamino or halo.

The term "heterocyclooxy" denotes a heterocyclic group bonded through an oxygen bridge.

The term "heteroaryl" refers to an aromatic heterocycle, for example monocyclic or bicyclic aryl, such as pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzofuryl, and the like, optionally substituted by e.g. lower alkyl, lower alkoxy or halo.

The term "heteroarylsulfonyl" refers to heteroaryl-$S(O)_2$-.

The term "heteroaroyl" refers to heteroaryl-C(O)-.

The term "heteroaroylamino" refers to heteroaryl-C(O)NH-

The term "heteroaralkyl" refers to a heteroaryl group bonded through an alkyl group.

The term "heteroaralkanoyl" refers to heteroaralkyl-C(O)-.

The term "heteroaralkanoylamino" refers to heteroaralkyl-C(O)NH-.

The term "acyl" refers to alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl and the like.

The term "acylamino" refers to alkanoylamino, aroylamino, heteroaroylamino, aralkanoylamino, heteroaralkanoylamino and the like.

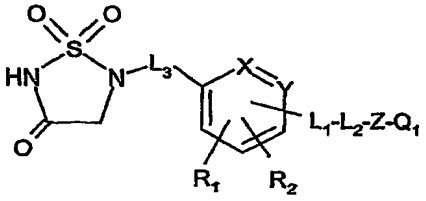
Preferred are the compounds of formula I wherein

Q_2 is oxygen;

X and Y are CH; or

-X=Y- is sulfur; or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Further preferred are the compounds of the formula



(IA)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy, aryloxy, heteroaralkyl or heteroaralkoxy;

R_2 is hydrogen; or

R_2 is $-C(O)R_3$ wherein

R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

L_1 is a single bond; or

L_1 is carbon which combined together with R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is CH or nitrogen which taken together with R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur; or

L_1 is CH, oxygen, sulfur or nitrogen provided L_2 is carbon which combined together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is $-CH_2-$, oxygen, sulfur or $-NR_6-$ provided L_2 is CH which taken together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl; or

L_2 is $-(CHR_7)_n-$ wherein

R_7 is hydrogen;

n is zero or an integer of 1 or 2;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen or optionally substituted alkyl;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(a) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl provided that Q_1 is not hydrogen when

R_1 and R_2 are hydrogen;

X and Y are CH;

L_1 is a single bond;

L_2 is $-(CHR_7)_n-$ wherein R_7 is hydrogen and n is zero;

Z is $-(CHR_8)_m-$ wherein R_8 is hydrogen and m is zero; and

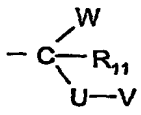
L_3 is $-(CHR_7)_s-$ wherein R_8 is hydrogen and s is 1;

(b) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are as defined for R_3;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

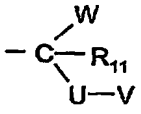
U is $-C(O)-$ or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

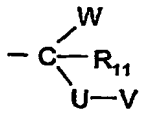
R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero; or

(e) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is $-NR_4R_5$, and R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

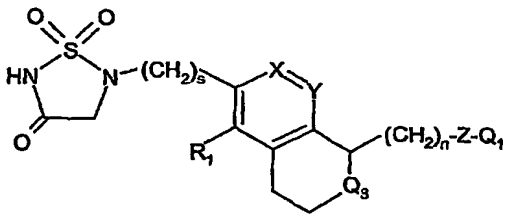
L_3 is $-(CHR_7)_s-$ wherein

R_7 is as defined for L_2;

s is an integer from 1 to 3;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula IA of the formula



(IB)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy, aryloxy, heteroaralkyl or heteroaralkoxy;

n is zero or an integer of 1 or 2;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

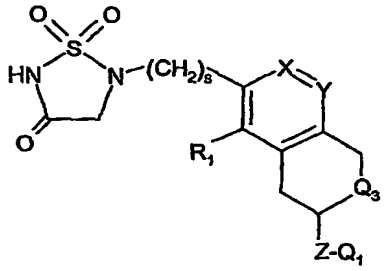
s is an integer of 1 or 2;

Q_3 is O, S or $-NR_6-$ wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula IA of the formula



(IC)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy, aryloxy, heteroaralkyl or heteroaralkoxy;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

s is an integer of 1 or 2;

Q_3 is O, S or $-NR_6-$ wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula IA wherein

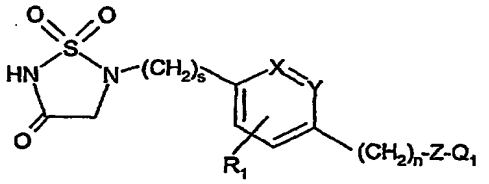
R_2 is hydrogen;

L_1 is a single bond;

L_2 is $-(CH_2)_n-$ wherein n is zero or an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Further preferred are the compounds of formula IA of the formula



(ID)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy or aryloxy;

n is zero or an integer of 1 or 2;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(a) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl provided that Q_1 is not hydrogen when

R_1 is hydrogen;

X and Y are CH;

n is zero;

Z is $-(CHR_8)_m-$ wherein m is zero; and

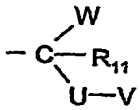
L_3 is $-(CH_2)_s-$ wherein s is 1;

(b) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

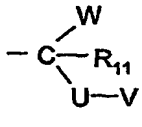
U is $-C(O)-$ or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ provided that

n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

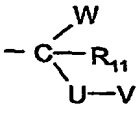
R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$ provided that

n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero; or

(e) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_r-$ in which r is zero or 1;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is $-NR_4R_5$ provided that

n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

s is 1;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

-X=Y- is sulfur;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

R_1 is bromide;

X and Y are CH;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is zero;

Z is $-(CH_2)_m-$ in which m is zero;

Q is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_mO(CH_2)_r-$ or $-(CH_2)_mS(CH_2)_r-$ wherein

m is zero;

r is zero or 1;

Q_1 is optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_mNR_9(CH_2)_r-$ wherein

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl or acyl;

m is zero;

r is zero or 1;

Q_1 is optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

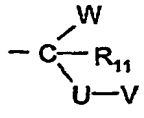
q is an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

U is -C(O)- or $-(CH_2)_r-$ in which r is zero;

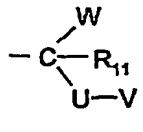
V is aryl, heteroaryl, optionally substituted alkyl or cycloalkyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is 1;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is $-NR_4R_5$, and R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen;

U is $-(CH_2)_p-$ in which p is zero;

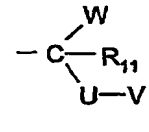
V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is 1;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is $-NR_4R_5$, and R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen;

U is $-(CH_2)_p-$ in which p is zero;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl or alkoxy; or R_{12} is $-NR_4R_5$;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Particular embodiments of the invention are:
5-Naphthalen-1-ylmethyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
N-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide;
[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-carbamic acid tert-butyl ester;
5-(4-Aminomethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-carbamic acid tert-butyl ester;

3-Phenyl-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-propionamide;

5-(3-Iodo-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Amino-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

N-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide;

1,1-Dioxo-5-pyridin-4-ylmethyl-1,2,5-thiadiazolidin-3-one;

5-(4-Amino-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

N-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-butyramide;

1-Propyl-3-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-urea;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

5-(2-Methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-pyridin-3-ylmethyl-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-pyridin-2-ylmethyl-1,2,5-thiadiazolidin-3-one;

5-(6-Amino-pyridin-3-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-thiophen-2-ylmethyl-1,2,5-thiadiazolidin-3-one;

5-(4-Methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Amino-2-bromo-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide;

N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-methanesulfonamide;

N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-methanesulfonamide;

5-(4-Methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

Amino-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetic acid;

2-Amino-N-propyl-2-[2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide;

2-Amino-N-propyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide;

2,2,2-Trifluoro-N-{propylcarbamoyl-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-methyl}-acetamide;

2-Methanesulfonylamino-N-propyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide;

2-Acetylamino-N-propyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-propionamide;

2-Acetylamino-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-malonic acid diethyl ester;

2-Amino-N-propyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-propionamide;

2-Acetylamino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-propionic acid ethyl ester;

Phenyl-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-acetic acid;

1,1-Dioxo-5-phenethyl-1,2,5-thiadiazolidin-3-one;

5-[2-(4-Methyl-thiazol-5-yl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-(3,4-Dimethoxy-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-(2-Chloro-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-(4-Amino-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2,2,2-Trifluoro-N-{4-[2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-ethyl]-phenyl}-acetamide;

N-{4-[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-ethyl]-phenyl}-butyramide;

1,1-Dioxo-5-(2-pyridin-3-yl-ethyl)-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(2-pyridin-4-yl-ethyl)-1,2,5-thiadiazolidin-3-one;

3-Phenyl-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-propionic acid;

5-[2-(3-Amino-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Aminomethyl-naphthalen-1-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(1-Ethyl-2-methyl-1H-benzimidazol-5-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-Methyl-1-(3-methyl-butyl)-1H-benzimidazol-5-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Methoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Isobutoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

{(1-Butylcarbamoyl-3-phenyl-propyl)-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[Butylcarbamoyl-(4-ethyl-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[Butylcarbamoyl-(3-phenoxy-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[Butylcarbamoyl-(4-methoxy-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[(2-Bromo-phenyl)-butylcarbamoyl-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

(Butylcarbamoyl-naphthalen-2-yl-methyl)-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[Butylcarbamoyl-(4-chloro-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[(3-Benzyloxy-phenyl)-butylcarbamoyl-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{((E)-1-Butylcarbamoyl-3-phenyl-allyl)-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

N-(1-Butylcarbamoyl-3-phenyl-propyl)-N-(4-(1,1,4-trioxo-1,2,5-thiazodiazolidin-2-ylmethyl)-benzoyl)-amino-acetic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methanesulfonyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-chloro-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-butyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-hydroxymethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-phenethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid biphenyl-2-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-difluoromethoxy-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-(carboxy-difluoro-methyl)-thiophen-2-ylmethyl ester;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenylmethanesulfonyl]-acetic acid ethyl ester;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylsulfanyl]-acetic acid ethyl ester;

5-[4-(3-Methyl-butylsulfanylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-ethyl-butyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid cyclobutylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid cyclopentylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methyl-pentyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2,4,4-trimethyl-pentyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid cyclohexylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 1,2-dimethyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid cyclopentyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methyl-butyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methylsulfanyl-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-carboxymethylsulfanyl-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-nitro-furan-2-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid pyridin-2-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-hydroxymethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-methanesulfonyl-benzyl ester;

(4-{4-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoylamino]-butyl}-phenyl)-acetic acid;

(4-{3-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoylamino]-propyl}-phenyl)-acetic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-dimethylaminomethyl-furan-2-ylmethyl ester;

(S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-ethyl}-3-phenyl-propionamide;

5-(1H-Indol-5-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(3,4,5-trimethoxy-benzyl)-1,2,5-thiadiazolidin-3-one;

5-[4-(4-Benzyl-piperazin-1-ylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetic acid;

5-(4-Benzoyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-Naphthalen-2-ylmethyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[4-(4-Methyl-pentanoyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[3-(2-Fluoro-phenoxy)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

3-{2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-ethoxy}-benzoic acid;

1-(3-Methyl-butyl)-6-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-1H-quinolin-2-one;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid methyl-phenethyl-amide;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid (2-thiophen-2-yl-ethyl)-amide;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid phenethyl-amide;

[4-(2-{[5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carbonyl]-amino}-ethyl)-phenyl]-acetic acid;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid 4-carboxy-benzyl ester;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid isobutyl ester;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid isobutyl-amide;

2-Amino-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide;

4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxy-benzyl ester;

1,1-Dioxo-5-(3-phenoxy-benzyl)-1,2,5-thiadiazolidin-3-one;

3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

5-(4-1ydroxymethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester;

5-(4-1ydroxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-Nitro-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

5-Amino-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

5-(4-Chloro-3-methoxy-5-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(2-Nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Methyl-2-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(3-phenyl-propyl)-1,2,5-thiadiazolidin-3-one;

5-(4-Butoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(2-trifluoromethyl-benzyl)-1,2,5-thiadiazolidin-3-one;

3-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

4-[5-Amino-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-butyric acid;

5-(2-Methyl-3-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Methyl-3-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(5-Methyl-2-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(2-Amino-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-isoindole-1,3-dione;

2-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-isoindole-1,3-dione;

5,5'-[1,4-phenylenebis(methylene)bis[1,2,5-Thiadiazolidine-3-one], 1,1-dioxide;

N-[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-oxalamic acid;

5-(3-1ydroxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

5-[5-(4-Nitro-phenyl)-furan-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Fluoro-2-trifluoromethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-1ydroxymethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Amino-5-hydroxymethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Amino-4-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(2-Amino-3-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Amino-2-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(2-Amino-5-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2,2,2-Trifluoro-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-pyridine-2-carbonitrile;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-pyridine-2-carboxylic acid ethyl ester;

5-(3,4-Dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Amino-5-hydroxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3,5-Dimethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

(S)-3-Phenyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-propionic acid ethyl ester;

(S)-3-Phenyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-propionic acid ethyl ester;

2-Amino-5-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester;

2-Acetylamino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester;

5-(2-Benzyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(2,4-Bis-trifluoromethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(2,4,6-trifluoro-benzyl)-1,2,5-thiadiazolidin-3-one;

5-(2-Bromo-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5,5'-[[1,1'-biphenyl]-2,2'-diyl]bis(methylene)bis[1,2,5-Thiadiazolidine-3-one], 1,1-dioxide;

5-(4-Ethylaminomethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2-Acetylamino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid ethyl ester;

1,1-Dioxo-5-[4-(phenethylamino-methyl)-benzyl]-1,2,5-thiadiazolidin-3-one;

5-(4-Diethylaminomethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid benzyl ester;

N-Benzyl-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide;

5-(5-Dimethylaminomethyl-furan-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

N-[2-(3-Trifluoromethyl-phenyl)-ethyl]-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide;

N-(3-Methyl-butyl)-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide;

(S)-3-Phenyl-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-propionic acid;

(R)-3-Phenyl-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-propionic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid benzyl ester;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid isobutyl ester;

2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid isobutyl ester;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid methyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxymethoxy-benzyl ester;

5-(5-Aminomethyl-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-{2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-ethyl}-benzoic acid;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid isobutyl ester;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid benzyl ester;

N-Isobutyl-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide;

5-(5-Diethylaminomethyl-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(2-{[5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophen-2-ylmethyl]-amino}-ethyl)-benzoic acid;

3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester;

3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid ethyl ester;

3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid isobutyl ester;

5-(4-Ethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(3-trifluoromethyl-benzyl)-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxymethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid phenethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-phenylamino-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-(3-methoxy-phenyl)-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2,2-dimethyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methoxycarbonyl-2-methyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2,2,4-trimethyl-pentyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-dimethylamino-2,2-dimethyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid (3aR,4S,5R,6aS)-5-benzoyloxy-2-oxo-hexahydro-cyclopenta[b]furan-4-ylmethyl ester;

6-{[5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophen-2-ylmethyl]-amino}-hexanoic acid;

5-{5-[(3-Methyl-butylamino)-methyl]-thiophen-2-ylmethyl}-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-methyl-4-nitro-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-chloro-4-methyl-benzyl ester;

5-[5-(Isobutylamino-methyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-ethoxycarbonyl-pentyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-(3-chloro-phenyl)-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-m-tolyl-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-(3-trifluoromethyl-phenyl)-ethyl ester;

(R)-3-Phenyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-propionic acid ethyl ester;

5-[4-(Benzylamino-methyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methyl-benzyl ester;

4-Methyl-6-{[5-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophen-2-ylmethyl]-amino}-hexanoic acid;

4-[(1,1,4-trioxido-1,2,5-thiadiazolidin-2-yl)methyl]-benzoic acid [4-(methoxycarbonyl)-phenyl]methyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-cyclohexyl-2-methyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-phenoxy-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-trifluoromethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-trifluoromethyl-benzyl ester;

4-[(1,1,4-trioxido-1,2,5-thiadiazolidin-2-yl)methyl]-benzoic acid 2-(4-carboxyphenyl)ethyl ester;

5-[5-(3-Methyl-butyryl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

3-[[[4-[(1,1,4-Trioxido-1,2,5-thiadiazolidin-2-yl)methyl]benzoyl]-oxy]methyl]benzoic acid;

5-[4-(Isobutylamino-methyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-{4-[(2,2-Dimethyl-propylamino)-methyl]-benzyl}-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid naphthalen-1-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-nitro-benzyl ester;

(4-{2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoylamino]-ethyl}-phenyl)-acetic acid;

5-[5-(4-Methyl-pentanoyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-nitro-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-(carboxymethyl-amino)-2,2-dimethyl-propyl ester;

5-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyloxymethyl]-thiophene-2-carboxylic acid;

5-[4-(4-Benzyl-piperazin-1-ylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid biphenyl-4-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-acetylamino-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-benzyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methyl-3-nitro-benzyl ester;

Glycine, N-(aminosulfonyl)-N-[[4-[[(2-phenylethyl)thio]methyl]phenyl]methyl]-, methyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-carboxymethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methyl-3-nitro-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-fluoro-2-trifluoromethyl-benzyl ester;

4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-methyl-2-nitro-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid o-tolyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-(carboxymethyl-methyl-amino)-2,2-dimethyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid phenyl ester

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-isobutylcarbamoyl-thiophen-2-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid naphthalen-2-ylmethyl ester;

N,N-Diisobutyl-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide;

{4-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-piperazin-1-yl}-acetic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid naphthalen-2-yl ester;

5-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyloxymethyl]-thiophene-2-carboxylic acid isobutyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-carbamoyl-thiophen-2-ylmethyl ester;

5-[4-(4-Benzyl-piperazine-1-carbonyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-(3-phenyl-propionyl)-thiophen-2-ylmethyl ester; and

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-benzylcarbamoyl-thiophen-2-ylmethyl ester; or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

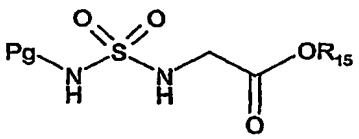
Pharmaceutically acceptable salts of any acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethylammonium, diethylammonium, and tris(hydroxymethyl)methyl-ammonium salts and salts with amino acids.

Similarly acid addition salts, such as of mineral acids, organic carboxylic, and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are possible provided a basic group, such as pyridyl, constitutes part of the structure.

Prodrug derivatives of any compound of the invention are derivatives of said compounds which following administration release the parent compound in vivo via some chemical or physiological process, e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the parent compound. Exemplary prodrug derivatives are, e.g., esters of free carboxylic acids and S-acyl and O-acyl derivatives of thiols, alcohols or phenols, wherein acyl has a meaning as defined herein. Preferred are pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, e.g., lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono or disubstituted lower alkyl esters such as the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester, and the like conventionally used in the art.

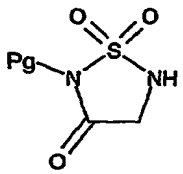
The compounds of the invention depending on the nature of the substituents, may possess one or more asymmetric centers. The resulting diastereoisomers, enantiomers and geometric isomers are encompassed by the instant invention.

Compounds of formula I may be prepared by cyclizing compounds of the formula



(II)

wherein Pg is an appropriate N-protecting group such as 4-methoxybenzyl, 2,4-dimethoxybenzyl or 2-trimethylsilylethyl, and R_{15} is hydrogen to afford compounds of the formula



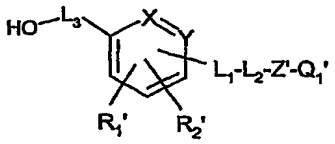
(III)

wherein Pg has a meaning as defined herein above, by treatment with a coupling agent such as diisopropyl carbodiimide (DIC) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) in the presence a base such as triethylamine (TEA) or N-methyl-morpholine (NMM) in an organic solvent such as tetrahydrofuran (THF), N,N-dimethyl-formamide (DMF) or dichoromethane (CH_2Cl_2). The reaction may be carried out in the presence of an additive such as of hydroxybenzotriazole (HOBt).

Compounds of formula II wherein R_{15} is an alkyl group such as methyl, ethyl or t-butyl and the like may be obtained analogously to a literature procedure described by Ducry, L.; Reinelt, S.; Seiler, P.; Diederich, F. *Helvetica Chimica. Acta* **1999**, *82*, 2432-47.

Compounds of formula II wherein R_{15} is an alkyl group as defined herein above may be converted to compounds of formula II wherein R_{15} is hydrogen according to methods well known in the art, e.g. compounds of formula II in which R_{15} is methyl or ethyl can be treated with aqueous base such as sodium or potassium hydroxide in an organic solvent such as THF, 1,4-dioxane, methanol (MeOH) or ethanol (EtOH) to afford compounds of formula II wherein R_{15} is hydrogen, or compounds of formula II in which R_{15} is t-butyl may be treated with an acid such as hydrochloric acid (HCl) or trifluoroacetic acid (TFA) in an organic solvent such as CH_2Cl_2 or ethyl acetate (EtOAc) to afford compounds of formula II wherein R_{15} is hydrogen.

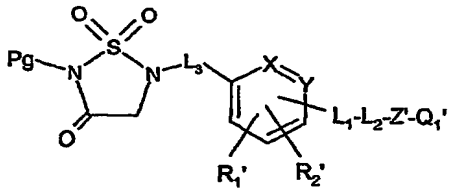
Compounds of formula III wherein Pg has a meaning as defined herein may be condensed with a variety of alcohols of the formula



(IV)

wherein L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to

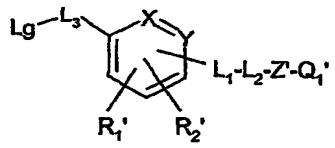
R_1, R_2, Z and Q_1, respectively, under Mitsunobu conditions, e.g., in the presence of reagents such as triphenylphosphine and diethylazodicarboxylate in a organic solvent such as THF to form compounds of the formula



(V)

wherein Pg, L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively.

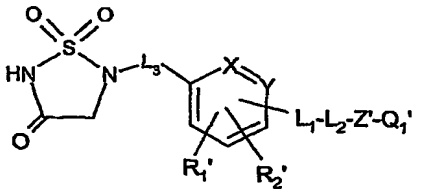
Alternatively, compounds of formula III wherein Pg has a meaning as defined herein, may be condensed with alkylating agents of the formula



(VI)

wherein Lg represents a leaving group, such as bromide, chloride, methanesulfonate or trifluoromethanesulfonate, and L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, in the presence of a base such as 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) in an inert solvent such as CH_2Cl_2, THF or DMF to afford compounds of formula V.

Compounds of formula V wherein Pg, L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, can be converted to compounds of the formula

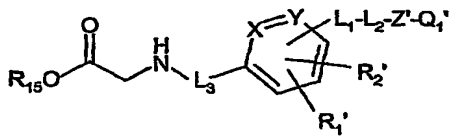


(I')

by removal of the N-protecting group according to methods well known in the art, e.g. in particular when Pg is 4-methoxybenzyl or 2,4-dimethoxybenzyl group using hydrogen in the

presence of a catalyst such as palladium on carbon in a polar organic solvent such as MeOH or EtOAc, or by treatment with an acid such as TFA in an organic solvent such as CH_2Cl_2, preferably in the presence of an additive such as t-butyldimethylsilane or triethylsilane, or in particular when Pg is 2-trimethylsilylethyl group using a fluoride reagent such as tetra-n-butylammoniumfluoride in an organic solvent such as THF or 1,4-dioxane.

In addition, compounds of formula I' wherein L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, may be prepared by condensing compounds of the formula

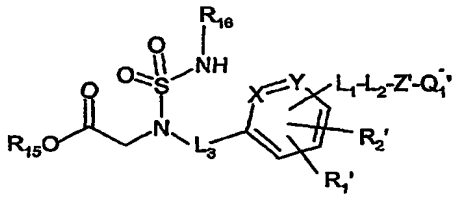


(VII)

wherein R_{15} has a meaning as defined herein above, with sulfamoyl chloride analogs of the formula

$$ClS(O)_2NHR_{16} \qquad \text{(VIII)}$$

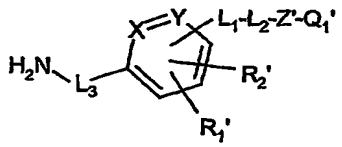
wherein R_{16} is hydrogen or alkoxycarbonyl such as t-butoxycarbonyl or 2-trimethylsilyl-ethoxycarbonyl in the presence of a base such as TEA or NMM in an organic solvent such as acetonitrile (MeCN), CH_2Cl_2 or THF to form compounds of the formula



(IX)

wherein R_{15}, R_{16}, L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively. Compounds of formula VIII wherein R_{16} is alkoxycarbonyl may be obtained by reacting chlorosulfonyl isocyanate with the appropriate alcohol in an organic solvent such as MeCN, CH_2Cl_2 or THF.

Compounds of formula VII may be prepared using methods well known in the art or according to methods described herein or modifications thereof, e.g., according to the method described by Tohru Fukuyama et. al., *Tet. Lett.* **1997**, *38* (33), 5831-34, or by reacting amines of the formula



(X)

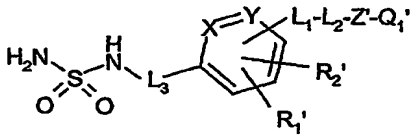
wherein L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, with acetates of the formula

$$Lg\text{-}CH_2\text{-}C(O)\text{-}O\text{-}R_{15} \qquad (XI)$$

wherein Lg and R_{15} have meanings as defined herein, in the presence of a base such as TEA or NMM in an inert solvent such as THF or 1,4-dioxane.

Compounds of formula IX wherein R_{15}, L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, and R_{16} is alkoxycarbonyl may be converted to compounds of formula IX wherein R_{16} is hydrogen according to methods known in the art or using methods described herein or modifications thereof, e.g., compounds of formula IX wherein R_{16} is t-butoxycarbonyl may be treated with an acid such as TFA, neat or in an organic solvent such as CH_2Cl_2, or compounds of formula IX wherein R_{16} is 2-trimethylsilylethoxycarbonyl may be treated with a fluoride reagent such as tetra-n-butylammoniumfluoride in an organic solvent such as THF or 1,4-dioxane to afford compounds of formula IX wherein R_{16} is hydrogen.

Alternatively, compounds of formula IX wherein R_{15}, L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, and R_{16} is hydrogen, may be obtained by first condensing amines of formula X with sulfamide in an aqueous solution and in the presence of a base such as sodium bicarbonate ($NaHCO_3$) at an elevated temperature, preferably at the boiling point of the solution, to afford compounds of the formula



(XII)

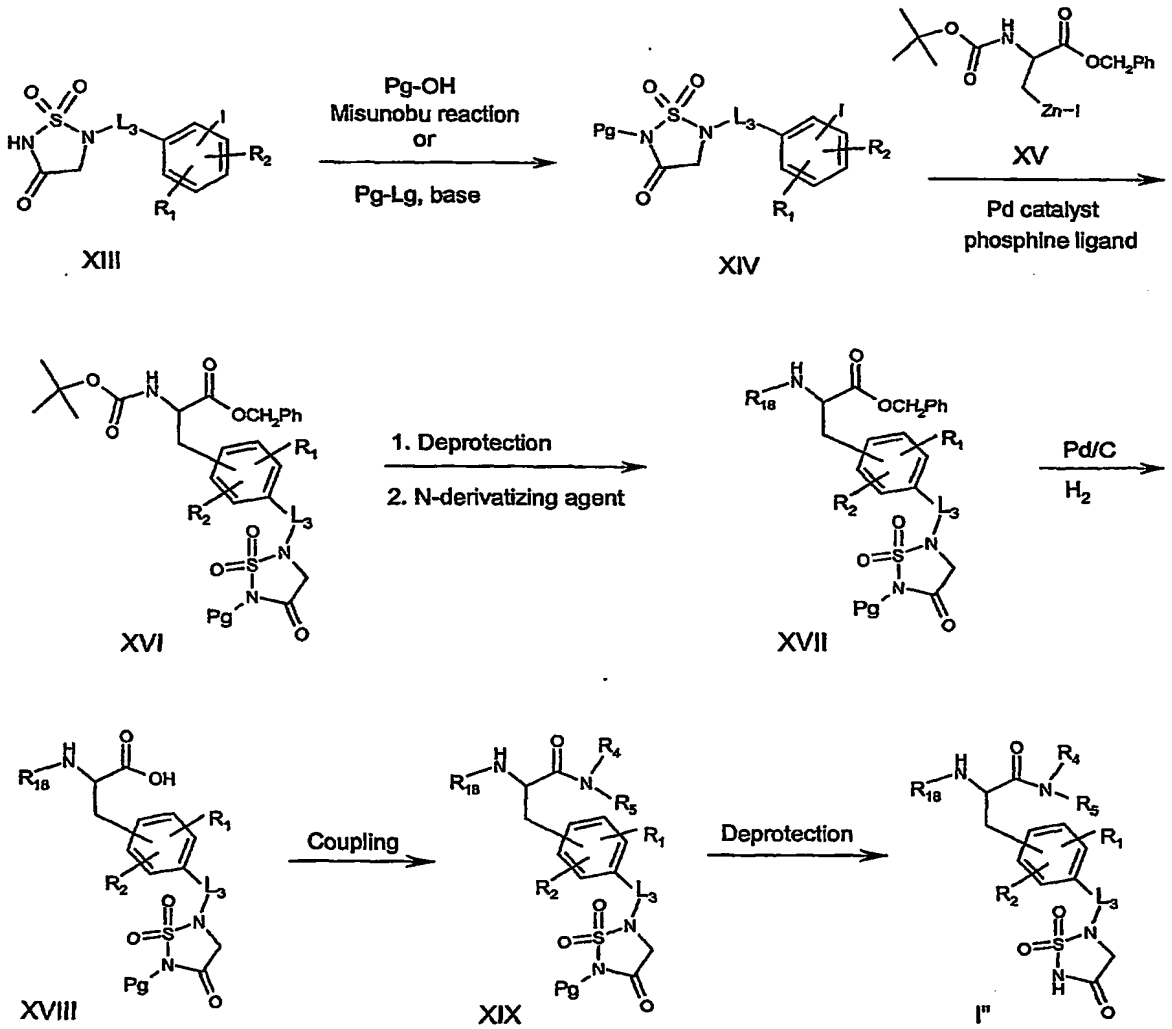
wherein R_{15}, L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively. Compound of formula XII may then be converted to

compound of formula IX in which R_{18} is hydrogen by the reaction with acetates of formula XI in the presence of a base such as sodium hydride in an inert solvent such as THF or DMF.

Compounds of formula IX wherein R_{15}, L_1, L_2, L_3, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, and R_{18} is hydrogen can be cyclized to form compounds of formula I' using methods and conditions well known in the art or as illustrated with Examples herein or modifications thereof.

In a particular embodiment of the invention, compounds of formula I may be prepared as illustrated in Scheme I.

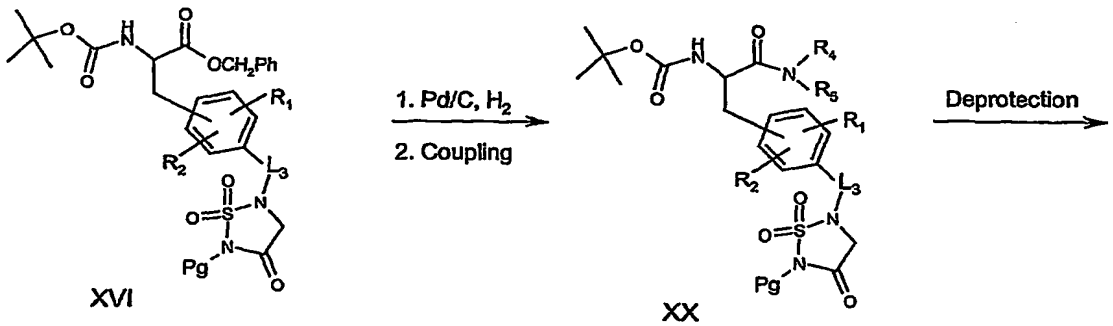
Scheme I



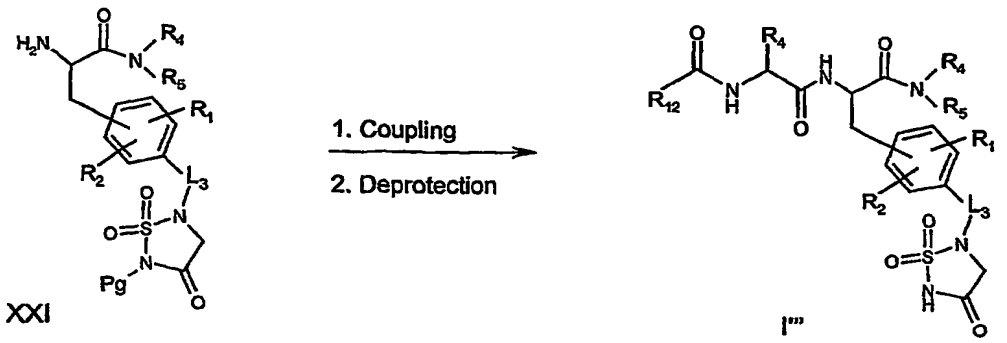
Compounds of formula XIII wherein R_1, R_2 and L_3 have meanings as defined herein, may be reacted with alcohols of the formula PgOH wherein Pg is a N-protecting group as defined herein under Mitsunobu conditions, e.g., in the presence of triphenylphoshine and diethyl azodicarboxylate in an organic solvent such as THF, to afford compounds of formula XIV. Alternatively, compounds of formula XIII may be converted to compounds of formula XIV by treatment with an alkylating agent of the formula Pg-Lg in which Pg and Lg have meanings as defined herein, in the presence of a base such as DBU in an inert solvent such as CH_2Cl_2, THF or DMF. The subsequent reaction between compounds of formula XIV and the organozinc reagent XV may be carried out in the presence of palladium(0) catalyst such as tris(dibenzylideneacetone)-dipalladium(0) acetate and a phosphine ligand such as tritolylphosphine in an organic solvent such as DMF to form compounds of formula XVI. Compounds of formula XVI may be treated with an acid such as TFA to remove the t-butoxycarbonyl protecting group. The resulting amines or acid addition salts thereof are then reacted with a N-derivatizing agent, such as an activated derivative of a carboxylic acid, a chloroformate, an isocyanate or a sulfonyl chloride in the presence of a base such as TEA, diisopropylethylamine or NMM in an inert solvent such as MeCN, CH_2Cl_2, DMF or THF to obtain compounds of formula XVII wherein R_{18} is $-C(O)R_5$, $-C(O)OR_5$, $-C(O)NR_4R_5$ or $-S(O)_2R_5$, respectively, and R_4 and R_6 have meanings as defined herein. The benzyl ester may be removed by catalytic hydrogenation to afford carboxylic acids of formula XVIII. Coupling of an activated derivative of a carboxylic acid of formula XVIII with amines of the formula HNR_4R_5 yields amides of formula XIX wherein R_4 and R_5 have meanings as defined herein. Finally, treatment with TFA affords compounds of formula I".

In another embodiment of the invention, compounds of formula I may be prepared as illustrated in Scheme II.

Scheme II



XVI XX



XXI

I'''

In the processes cited herein, activated derivatives of carboxylic acids, e.g., those of formula XVIII, include acid chlorides, bromides and fluorides, mixed anhydrides, lower alkyl esters, and activated esters thereof, and adducts formed with coupling agents such as EDCI, DIC, O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate and the like. Mixed anhydrides are preferably such from pivalic acid, or lower alkyl hemiesters of carbonic acids, such as ethyl or isobutyl analogs. Activated esters include, for example, succinimido, phthalimido or 4-nitrophenyl esters. The reaction of an activated derivative of a carboxylic acid, e.g., those of formula XVIII, with an amine may be carried out in the presence of a base such as TEA, diisopropylethylamine or NMM in an inert solvent such as CH_2Cl_2, DMF or THF. Carboxylic acids, e.g. those of formula XVIII, can be converted to their activated derivatives using methods described herein or modifications thereof or using methods well known in the art.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as amino, thiol, carboxyl, and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected amino, thiol, carboxyl, and hydroxyl groups are those that can be converted under mild conditions into free amino thiol, carboxyl and hydroxyl groups without the molecular framework being destroyed or other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxyl group, amino group, etc.), the structure and stability of the molecule of which the substituent is a part and the reaction conditions.

Well known protecting groups that meet these conditions and their introduction and removal are described, for example, in J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York, 1973, T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1991.

The above mentioned reactions are carried out according to standard methods, in the presence or absence of diluent, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures (preferably at or near the boiling point of the solvents used), and at atmospheric or super-atmospheric pressure. The preferred solvents, catalysts and reaction conditions are set forth in the appended illustrative Examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed in situ under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known per se.

The invention also relates to any novel starting materials, intermediates and processes for their manufacture.

Depending on the choice of starting materials and methods, the new compounds may be in the form of one of the possible isomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) isomers, optical isomers (antipodes), racemates, or mixtures thereof. The aforesaid possible isomers or mixtures thereof are within the purview of this invention.

Any resulting mixtures of isomers can be separated on the basis of the physico-chemical differences of the constituents, into the pure geometric or optical isomers, diastereoisomers, racemates, for example by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g. by separation of the diastereoisomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. The carboxylic acid intermediates can thus be resolved into their optical antipodes e.g. by fractional crystallization of d- or l-(alpha-methylbenzylamine, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydroabietylamine, brucine or strychnine)-salts. Racemic products can also be resolved by chiral chromatography, e.g. high pressure liquid chromatography using a chiral adsorbent.

Finally, compounds of the invention are either obtained in the free form, as a salt thereof if salt forming groups are present or as prodrug derivatives thereof.

Compounds of the instant invention which contain acidic groups, in particular the NH group of the 1,1-dioxo-1,2,5-thiadiazolidin-3-one moiety, may be converted into salts with pharmaceutically acceptable bases. Such salts include alkali metal salts like sodium. lithium and potassium salts, alkaline earth metal salts like calcium and magnesium salts, ammonium salts with organic bases, e.g., trimethylamine salts, diethylamine salts, tris(hydroxymethyl)methylamine salts, dicyclohexylamine salts and N-methyl-D-glucamine salts, salts with amino acids like arginine, lysine, and the like. Salts may be formed using conventional methods, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. From the solutions of the latter, the salts may be precipitated with ethers, e.g. diethyl ether. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained.

Compounds of the invention having basic groups can be converted into acid addition salts, especially pharmaceutically acceptable salts. These are formed, for example, with inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric or hydrohalic acid, or with organic carboxylic acids, such as (C_1-C_4)-alkanecarboxylic acids which, for example, are unsubstituted or substituted by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, succinic, maleic or fumaric acid, such as hydroxycarboxylic acids, for example glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or with organic sulfonic acids, such as (C_1-C_4)-alkylsulfonic acids (for example methanesulfonic acid) or arylsulfonic

acids which are unsubstituted or substituted (for example by halogen). Preferred are salts formed with hydrochloric acid, methanesulfonic acid and maleic acid.

In view of the close relationship between the free compounds, the prodrug derivatives and the compounds in the form of their salts, whenever a compound is referred to in this context, a prodrug derivative and a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, to inhibit protein tyrosine phosphatases, and for the treatment of conditions associated with PTPase activity, in particular, PTP-1B activity. Such conditions include insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels. The compounds of the present invention may also be employed in the treatment, prevention or control of a number of conditions that accompany Type 2 diabetes, including hyperlipidemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, irritable bowel syndrome, pancreatitis, adipose cell tumors and carcinomas such as liposarcoma, dyslipidemia, and other disorders where insulin resistance is indicated. In addition, the compounds of the present invention may be employed to treat or prevent cancer, osteoporosis, neurodegenerative and infectious diseases, and diseases involving inflammation and the immune system. The said pharmaceutical compositions comprise a therapeutically effective amount of a pharmacologically active compound of the instant invention, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising a therapeutically effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose

and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbants, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to75%, preferably about 1 to 50%, of the active ingredient.

Suitable formulations for transdermal application include a therapeutically effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

The pharmaceutical formulations contain a therapeutically effective amount of a compound of the invention as defined above, either alone or in a combination with another therapeutic agent, e.g., each at an effective therapeutic dose as reported in the art. Such therapeutic agents include insulin, insulin derivatives and mimetics, insulin secretagogues such as the sulfonylureas, e.g., Glipizide and Amaryl, insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide, PPARα and/or PPARγ ligands, biguanides such as metformin, aldose reductase inhibitors, alpha-glucosidase inhibitors such as acarbose, glycogen phosphorylase inhibitors, GLP-1, GLP-1 analogs such as Exendin-4 and GLP-1 mimetics, and DPP-IV inhibitors. Thus, the methods of treatment or prevention described herein may further include administering to mammals a second anti-diabetic compound in an amount effective to treat or prevent diabetes. Similarly, the methods of treatment of diabetes may include the administration of a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor such as lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin, fluidostatin and rivastatin, a squalene synthase inhibitor or FXR and LXR ligands, cholestyramine, fibrates, nicotinic acid, and aspirin in an

amount effective to improve the lipid profile. The combination of a cholesterol lowering agent, anti-hypertensive agent or anti-obesity agent with a PTPase inhibitor, in particular a PTP-1B inhibitor, may be beneficial in the treatment or prevention of atherosclerosis, hypertension, obesity and other conditions that often are associated with Type 2 diabetes. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

A unit dosage for a mammal of about 50 to 70 kg may contain between about 1 mg and 1000 mg, advantageously between about 5 mg to 500 mg of the active ingredient. The therapeutically effective dosage of a compound of formula I is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, on the form of administration, and on the compound involved.

The compounds of the present invention are inhibitors of PTPases, in particular PTP-1B, and thus may be employed for the treatment of conditions associated with PTPase activity, in particular with PTP-1B activity, as described herein, e.g. insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels, and conditions that accompany Type 2 diabetes, including hyperlipidemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, irritable bowel syndrome, pancreatitis, adipose cell tumors and carcinomas such as liposarcoma, dyslipidemia, and other disorders where insulin resistance is a component. In addition, the compounds of this invention may be employed to treat or prevent cancer, osteoporosis, neurodegenerative and infectious diseases, and diseases involving inflammation and the immune system.

The above-cited properties are demonstrable in vitro and in vivo tests, using advantageously mammals, e.g. mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. Said compounds can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions, and in vivo either enterally, parenterally, advantageously intravenously, e.g. as a suspension or in aqueous solution. The dosage in vitro may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount in vivo may range depending on the route of administration, between about 1 and 500 mg/kg, preferably between about 5 and 100 mg/kg.

The activity of a compound according to the invention can be assessed by the following methods or methods well described in the art:

The PTP-1B inhibitory activity in vitro may be determined as follows:

Assessment of human PTP-1B (hPTP-1B) activity in the presence of various agents is determined by measuring the amount of inorganic phosphate released from a phosphopeptide substrate using a 96-well microtiter plate format. The assay (100 µL) is performed in an assay buffer comprised of 50 mM TRIS (pH 7.5), 50 mM NaCl, 3 mM DTT at ambient temperature. The assay is typically performed in the presence of 0.4% dimethyl sulfoxide (DMSO). However, concentrations as high as 10% are used with certain poorly soluble compounds. A typical reaction is initiated by the addition of 0.4 pmoles of hPTP-1B (amino acids 1-411) to wells containing assay buffer, 3 nmoles of the synthetic phosphopeptide substrate (GNGDpYMPMSPKS), and the test compound. After 10 min, 180 µL malachite green reagent (0.88 mM malachite green, 8.2 mM ammonium molybdate, aqueous 1 N HCl, and 0.01% Triton X-100) is added to terminate the reaction. Inorganic phosphate, a product of the enzyme reaction, is quantitiated after 15 min as the green color resulting from complexing with the Malichite reagent and is determined as an A_{620} using a Molecular Devices (Sunnyvale, CA) SpectraMAX Plus spectrophotometer. Test compounds are solubilized in 100 % DMSO (Sigma, D-8779) and diluted in DMSO. Activity is defined as the net change in absorbance resulting from the activity of the uninhibited $hPTP\text{-}1B_{[1\text{-}411]}$ minus that of a tube with acid-inactivated $hPTP\text{-}1B_{[1\text{-}411]}$.

The $hPTP\text{-}1B_{[1\text{-}411]}$ is cloned by PCR from a human hippocampal cDNA library (Clonetech) and inserted into a pET 19-b vector (Novagen) at the Nco1 restriction site. E. coli strain BL21 (DE3) is transformed with this clone and stored as a stock culture in 20% glycerol at –80° C. For enzyme production, a stock culture is inoculated into Lb/Amp and grown at 37°C. Expression of PTP-1B is initiated by induction with 1mM IPTG after the culture had reached an OD_{600} = 0.6. After 4h, the bacterial pellet is collected by centrifugation. Cells are resuspended in 70mL lysis buffer (50mM Tris, 100 mM NaCl, 5mM DTT, 0.1% Triton X-100, pH7.6), incubated on ice for 30 min then sonicated (4 X 10sec bursts at full power). The lysate is centrifuged at 100,000 x g for 60 min and the supernatant is buffer exchanged and purified on a cation exchange POROS 20SP column followed by an anion exchange Source 30Q (Pharmacia) column, using linear NaCl gradient elutions. Enzyme is pooled, adjusted to 1mg/mL and frozen at –80° C.

Competitive binding to the active site of the enzyme can be determined as follows:

Ligand binding is detected by acquiring ^{1}H-^{15}N HSQC spectra on 250 µL of 0.15 mM PTP-$1B_{[1-298]}$ in the presence and absence of added compound (1-2 mM). The binding is determined by the observation of ^{15}N- or ^{1}H-amide chemical shift changes in two dimensional HSQC spectra upon the addition of a compound to ^{15}N-label protein. Because of the ^{15}N spectral editing, no signal from the ligand is observed, only protein signals. Thus, binding can be detected at high compound concentrations. Compounds which caused a pattern of chemical shift changes similar to the changes seen with known active site binders are considered positive.

All proteins are expressed in E. coli BL21 (DE3) containing plasmids constructed using pET19b vectors (Novagen). Uniformly ^{15}N-labeled PTP-$1B_{1-298}$ is produced by growth of bacteria on minimal media containing ^{15}N-labeled ammonium chloride. All purification steps are performed at 4°C. Cells (~15 g) are thawed briefly at 37°C and resuspended in 50 mL of lysis buffer containing 50 mM Tris-HCl, 150 mM NaCl, 5 mM DTT, pH 8.0 containing one tablet of Complete (EDTA-free) protease cocktail (Boehringer Mannheim), 100 µM PMSF and 100 µg/mL DNase I. The cells are lysed by sonication. The pellet is collected at 35,000 x g, resuspended in 25 mL of lysis buffer using a Polytron and collected as before. The two supernatants are combined and centrifuged for 30 min at 100,000 x g. Diafiltration using a 10 kD MWCO membrane is used to buffer exchange the protein and reduce the NaCl concentration prior to cation exchange chromatography. Diafiltration buffer contained 50 mM MES, 75 mM NaCl, 5 mM DTT, pH 6.5. Soluble supernatant is then loaded onto a POROS 20 SP (1 x 10 cm) column equilibrated with cation exchange buffer (50 mM MES and 75 mM NaCl, pH 6.5) at a rate of 20 mL/min. Protein is eluted from the column using a linear salt gradient (75-500 mM NaCl in 25 CV). Fractions containing PTP-1B's are identified and pooled according to SDS-PAGE analyses. PTP-$1B_{1-298}$ is further purified by anion exchange chromatography using a POROS 20 HQ column (1 x 10 cm). The pool from cation exchange chromatography is concentrated and buffer exchanged in 50 mM Tris-HCl, pH 7.5 containing 75 mM NaCl and 5 mM DTT. Protein is loaded onto column at 20 mL/min and eluted using a linear NaCl gradient (75-500 mM in 25 CV). Final purification is performed using Sephacryl S-100 HR (Pharmacia)(50 mM HEPES, 100 mM NaCl, 3 mM DTT, pH 7.5). The NMR samples are composed of uniformly ^{15}N-labeled PTP-$1B_{1-298}$ (0.15 mM) and inhibitor (1-2 mM) in a 10%D_2O/90%H_2O Bis-Tris-d_{19} buffer (50 mM, pH = 6.5) solution containing NaCl (50 mM), DL-1, 4-Dithiothreitol-d_{10} (5mM) and Sodium azide (0.02%).

The ^{1}H-^{15}N HSQC NMR spectra are recorded at 20°C, on Bruker DRX500 or DMX600 NMR spectrometers. In all NMR experiments, pulsed field gradients are applied to

afford the suppression of solvent signal. Quadrature detection in the indirectly detected dimensions is accomplished by using the States-TPPI method. The data are processed using Bruker software and analyzed using NMRCompass software (MSI) on Silicon Graphics computers.

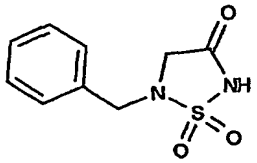
The glucose and insulin lowering activity in vivo may be evaluated as follows:

Adult male C57BL ob/ob mice (Jackson Lab, Bar Harbor, ME) at the age of 11 weeks are housed six per cage in a reversed light cycle room (light on from 6:00 p.m. to 6:00 a.m.) and given access to Purina rodent chow and water *ad libitum*. On day 1 tail blood samples are taken at 8:00 am and plasma glucose levels are determined. The animals are randomly assigned to the control and compound groups. The means of plasma glucose values of the groups are matched. Animals are then orally dosed with vehicle (0.5% carboxymethyl-cellulose with 0.2% Tween-80) or compounds (at 30 mg/kg) in vehicle. The mice are dosed daily for a total of 3 days. On day 4 basal blood samples are taken. The plasma samples are analyzed for glucose concentrations using a YSI2700 Dual Channel Biochemistry Analyzer (Yellow Springs Instrument Co., Yellow Springs, OH) and insulin concentrations using an ELISA assay.

The following Examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centrigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mmHg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g. microanalysis, melting point (mp) and spectroscopic characteristics (e.g. MS, IR, NMR). Abbreviations used are those conventional in the art. The concentration for $[\alpha]_D$ determinations is expressed in mg/mL.

Example 1

5-Benzyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one



A. N-Benzyl-N-sulfamidoglycine ethyl ester

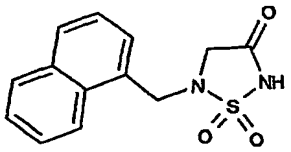
A solution of N-benzylglycine ethyl ester (6.47 g, 34.5 mmol) and TEA (10.47 g, 103 mmol) in MeCN (10 mL) is treated with a solution of sulfamoyl chloride (3.99 g, 34.5 mmol) in MeCN (20 mL) dropwise over 20 min.. The mixture is stirred for 3 h and filtered. The filtrate is concentrated and the residue is partitioned between EtOAc and aqueous 3N hydrochloric acid (HCl). The organic layer is washed with aqueous 3N HCl, saturated aqueous sodium chloride (NaCl) solution and dried over magnesium sulfate ($MgSO_4$). The solvent is evaporated to afford N-benzyl-N-sulfamidoglycine ethyl ester as a yellow oil: $[M-1]^-$ = 272.

B. 5-Benzyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one

Sodium hydride (9 mg, 0.367 mmol) is added to a solution of the title A compound, N-benzyl-N-sulfamidoglycine ethyl ester (100 mg, 0.367 mmol) in dry THF (5 mL) under N_2 atmosphere. The mixture is stirred at RT (RT) for 3 days. The mixture is acidified with 3N HCl in EtOAc. The solvents are evaporated and the residue is purified by C8 preparative reverse phase LC-MS chromatography using 5% → 100% MeCN in water over 13 minutes to afford 5-benzyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid: $[M-1]^-$ = 225.

Example 2

5-Naphthalen-1-ylmethyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one



A. N-(1-Naphthylmethyl)glycine ethyl ester

A solution of 1-aminomethylnaphthalene (2.15 g, 13.6 mmol) and TEA (1.65 g, 16.3 mmol) in CH_2Cl_2 (50 mL) is treated with ethyl bromoacetate (2.28 g, 13.6 mmol) dropwise over 90 min. The mixture is stirred at RT for 3 h and washed with water. The organic layer is dried over anhydrous $MgSO_4$ and concentrated. The residue is flash chromatographed on silica gel using CH_2Cl_2 → 1% MeOH in CH_2Cl_2 as the eluent to afford N-(1-naphthylmethyl)glycine ethyl ester as a yellow oil: $[M+1]^+$ = 244.

B. N-(1-Naphthylmethyl)-N-sulfamidoglycine ethyl ester

A solution of the title A compound, N-(1-naphthylmethyl)glycine ethyl ester (870 mg, 3.58 mmol) and TEA (1.09 g, 10.7 mmol) in MeCN (10 mL) is added dropwise over 10 min. to a solution of sulfamoyl chloride (825 mg, 7.15 mmol) in MeCN (10 mL). The mixture is

stirred for 16 h and the solvent is evaporated. The residue is partitioned between EtOAc and water. The organic layer is dried over $MgSO_4$ and concentrated. The residue is flash chromatographed on silica gel using 5% MeOH in CH_2Cl_2 as the eluent to afford N-(1-naphthyl-methyl)-N-sulfamidoglycine ethyl ester as a clear oil: $[M+1]^+ = 323$.

C. 5-Naphthalen-1-ylmethyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one

A solution of the title B compound, N-(1-naphthylmethyl)-N-sulfamidoglycine ethyl ester (180 mg, 0.558 mmol) in 5 mL of EtOH is treated with 1N aqueous NaOH (0.67 mL) and the mixture is stirred for 1 h at RT. The resulting precipitate is filtered, washed with EtOH and dried to give 5-naphthalen-1-ylmethyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one as the sodium salt: $[M-1]^- = 275$.

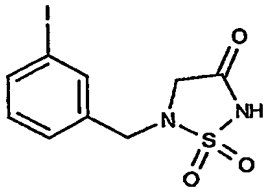
Example 3

The following examples are prepared analogously to Examples 1 and 2 using appropriately protected starting materials and standard reaction conditions.

Example	Chemical Name	MS [m/z]
3-1	N-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide	$[M-1]^- = 296$
3-2	[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-carbamic acid tert-butyl ester	$[M-1]^- = 354$
3-3	5-(4-Aminomethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^- = 254$
3-4	N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide	$[M-1]^- = 296$
3-5	[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-carbamic acid tert-butyl ester	$[M-1]^- = 354$
3-6	3-Phenyl-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-propionamide	$[M-1]^- = 386$

Example 4

5-(3-Iodobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one



A. N-(3-Iodobenzyl)glycine-N-sulfonic acid amide

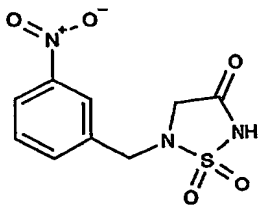
t-Butanol (0.354 mL, 3.7 mmol) is added dropwise by syringe to a solution of chlorosulfonyl isocyanate (0.322 mL, 3.7 mmol) in 46 mL of CH_2Cl_2 which is being stirred in an ice salt bath under an argon atmosphere. After 1.5 h, a solution of (3-iodo-benzylamino)-acetic acid t-butyl ester (1.07 g, 3.08 mmol) and TEA (1.55 mL, 11.1 mmol) in 46 mL of CH_2Cl_2 is added. When HPLC of a small aliquot revealed the complete disappearance of the amine (less than two h) 100 mL of 1N aqueous HCl is added to the reaction. The reaction mixture is extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers are dried by passing through a small column of sodium sulfate (Na_2SO_4), and evaporated to give a clear oil. This is purified by silica gel flash chromatography on a 35 g RediSep column with CH_2Cl_2 as the eluent. The pure fractions are combined and evaporated down to give an intermediate product which is dissolved in 6 mL of TFA and stirred for 2 h. The acid is removed by evaporation on a Savant SpeedVac to yield N-(3-iodobenzyl)-glycine-N-sulfonic acid amide as a white solid: $[M-1]^-$ = 369.

B. 5-(3-Iodobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

A solution of the title A compound, N-(3-iodobenzyl)glycine-N-sulfonic acid amide (459.2 mg, 1.24 mmol) in 12.4 mL of DMF is added dropwise over a period of 10 min to a solution of diisopropyl carbodiimide (0.194 mL, 1.24 mmol) stirred in 12.4 mL of CH_2Cl_2. After an additional 1.75 h, the reaction mixture is split into two 40 mL scintillation vials and evaporated down overnight on a Savant SpeedVac system. An attempt at purification using a 35 g RediSep Silica gel flash column with 20% EtOAc in hexane to 100% EtOAc gradient over 30 minutes failed, and the product is recovered from the column by elution with 10% MeOH in CH_2Cl_2. This material is concentrated and purified via reverse phase HPLC using a gradient from 10% to 90% MeCN in water over 5 min. Fractions containing the clean product are evaporated on a Savant SpeedVac system and 5-(3-iodobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one obtained as a white solid: mp = 101-103°C; $[M-1]^-$ = 351.

Example 5

5-(3-Nitrobenzyl)-1,1-dioxo-(1,2,5)thiadiazolidin-3-one



A. 3-Nitrobenzyl sulfamide

A solution of 3-nitrobenzylamine hydrochloride, (1.89 g, 10.0 mmol) in water (10 mL) is treated with sodium bicarbonate (840 mg, 10.0 mmol) and sulfamide, (960 mg, 10.0 mmol). The mixture is heated at reflux for 5 h. The cooled mixture is acidified to pH 2 with 1N aqueous HCl and the precipitate is filtered, washed with water and dried under vacuum at 50°C to afford 3-nitrobenzyl sulfamide as a tan solid: $[M-1]^-$ = 230.

B. N-(3-Nitrobenzyl)-N-sulfamidoacetic acid methyl ester

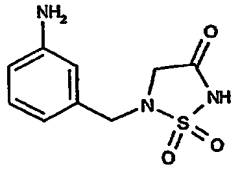
Sodium hydride (21 mg, 0.865 mmol) is added to a solution of the title A compound, 3-nitrobenzyl sulfamide in dry DMF (5 mL) under N_2 and the mixture is stirred for 20 min. Methyl bromoacetate (132 mg, 0.865 mmol) is added and the mixture is stirred at RT for 4 h. The solvent is evaporated and the residue is partitioned between EtOAc and aqueous saturated aqueous ammonium chloride (NH_4Cl) solution. The organic layer is evaporated and the residue is flash chromatographed on silica gel using 3% MeOH in CH_2Cl_2 as the eluent to afford N-(3-nitrobenzyl)-N-sulfamidoacetic acid methyl ester as a clear oil: $[M-1]^-$ = 302.

C. 5-(3-Nitrobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

Potassium bis(trimethylsilyl)amide (30 mg, 0.148 mmol) is added to a solution of the title B compound, N-(3-nitrobenzyl)-N-sulfamidoacetic acid methyl ester in dry THF under N_2 atmosphere. The mixture is stirred at RT for 16 h, acidified to pH 1 with 1N aqueous HCl and evaporated to dryness. The residue is purified by C8 preparative reverse phase LC-MS chromatography, from 5% to 100% MeCN in water over 13 min, and freeze-dried to afford 5-(3-nitrobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid: $[M-1]^-$ = 270.

Example 6

5-(3-Aminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

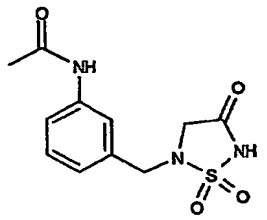


To a solution of the title C compound in Example 5, 5-(3-nitrobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (30 mg, 0.11 mmol) in EtOH (5 mL) is added palladium on carbon (10 mg) and the mixture is stirred under 1atm of hydrogen for 1 h. The catalyst is removed by filtration through a plug of Celite which is washed with MeCN/water (1:1), (20 mL). The

solvents are evaporated to afford 5-(3-Aminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a brown solid: $[M-1]^-$ = 240.

Example 7

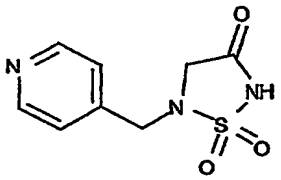
N-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)phenyl]acetamide



A solution of the title compound of Example 6, 5-(3-aminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (10 mg, 0.041 mmol) in acetic acid (AcOH, 5 mL) is treated with acetic anhydride (85 mg, 0.83 mmol) and stirred at RT for 72 h. The mixture is stirred with water for 2 h, then concentrated to dryness. The crude mixture is purified by LC/MS to afford N-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)phenyl]acetamide: $[M-1]^-$ = 282.

Example 8

1,1-Dioxo-5-pyridin-4-ylmethyl-1,2,5-thiadiazolidin-3-one



A. Glycine-N-sulfonic acid 4-methoxybenzylamide

Glycine methyl ester-N-sulfonic acid 4-methoxybenzylamide (3.03 g, 10.5 mmol, prepared analogously to literature procedure as described by Ducry, L.; Reinelt, S.; Seiler, P.; Diederich, F. *Helvetica Chimica. Acta.* **1999**, *82*, 2432-47) is dissolved in 80 mL of 1,4-dioxane, then added 20 mL of water, followed by 21 mL of 1N aqueous NaOH solution. After 40 minutes, the 1,4-dioxane is evaporated on the rotary evaporator, and the remaining aqueous solution is extracted with Et_2O. The aqueous solution is acidified with 1N aqueous HCl solution and extracted with EtOAc 2 times. The organic layer is dried over anhydrous Na_2SO_4, filtered and evaporated to dryness giving glycine-N-sulfonic acid 4-methoxybenzylamide: $[M-1]^-$ = 273.

B. 2-(4-Methoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title A compound, glycine-N-sulfonic acid 4-methoxybenzylamide (2.51 g, 9.2 mmol) is dissolved in 160 mL of THF, then HOBt (1.41 g, 9.2 mmol) is added as a solid and stirred until dissolved. EDCI (1.76 g, 9.2 mmol) is added as a solid and stirred for 10 minutes, followed by the addition of TEA (1.42 mL, 10.2 mmol). The reaction is stirred for 16 h, then evaporated down on the rotary evaporator. The residue is partitioned between 1N aqueous HCl and EtOAc. The organic layer is washed with aqueous saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gives an oil which solidifies on standing. This is dissolved in hot EtOAc, concentrated back down to 20 mL, filtered to remove solids and flash chromatographed on silica gel with 40% EtOAc in hexanes to afford 2-(4-methoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid: mp = 111-113°C; $[M-1]^-$ = 255.

C. 2-(4-Methoxybenzyl)-1,1-dioxo-5-pyridin-4-ylmethyl-1,2,5-thiadiazolidin-3-one

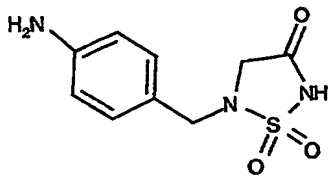
The title B compound, 2-(4-methoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (128 mg, 0.5 mmol), 4-hydroxypyridine (109 mg, 1 mmol), and triphenylphosphine (262 mg, 1 mmol) are put into a small reaction vessel under argon and dissolved in 10 mL of THF. This solution is stirred in an ice/water bath and diethylazodicarboxylate (174 mg, 1 mmol) diluted with an equal volume of THF is added dropwise to the stirred cold solution. The reaction is allowed to stir 16 h while the ice bath slowly warms to RT. The solvent is evaporated on the rotary evaporator, then the residue is taken up in a minimal amount of CH_2Cl_2 and chromatographed on a 10 g RediSep silica gel chromatography column, using a gradient from 1 % to 5 % EtOAc in CH_2Cl_2 over 15 to 20 min to afford 2-(4-methoxybenzyl)-1,1-dioxo-5-pyridin-4-ylmethyl-1,2,5-thiadiazolidin-3-one: $[M+1]^+$ = 348.

D. 1,1-Dioxo-5-pyridin-4-ylmethyl-1,2,5-thiadiazolidin-3-one

The title C compound, 2-(4-methoxybenzyl)-1,1-dioxo-5-pyridin-4-ylmethyl-1,2,5-thiadiazolidin-3-one (73 mg, 0.21 mmol) is dissolved in a mixture of TFA (4.75 mL) and triethylsilane (0.25 mL) in a 20 mL scintillation vial with polyseal cap. This is heated in an 80°C oil bath for 16 h. The reaction solvents are removed by overnight evaporation on a Savant SpeedVac system. This gives a white solid which is dissolved in water and filtered through a 0.45 micron PTFE filter disc. The filtrate is collected and the water removed by lyophilization to give 1,1-dioxo-5-pyridin-4-ylmethyl-1,2,5-thiadiazolidin-3-one TFA salt as an amorphous white solid: $[M+1]^+$ = 228.

Example 9

5-(4-Aminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one



A. Glycine-N-sulfonic acid 2,4-dimethoxybenzylamide

Glycine methyl ester-N-sulfonic acid 2,4-dimethoxybenzylamide (14.9 g, 47.0 mmol, prepared analogously to the literature procedure as described by Ducry, L.; Reinelt, S.; Seiler, P.; Diederich, F. *Helvetica Chimica. Acta.* **1999**, *82*, 2432-47) is dissolved in 100 mL of 1,4-dioxane, then 94 mL of 1N aqueous NaOH solution is added. After 120 min, the 1,4-dioxane is evaporated on the rotary evaporator, and the remaining aqueous solution is extracted with Et_2O. The aqueous solution is acidified with 1N aqueous HCl and extracted with EtOAc. The organic layer is dried over anhydrous $MgSO_4$, filtered and evaporated to dryness giving glycine-N-sulfonic acid 2,4-dimethoxybenzylamide: $[M-1]^-$ = 303.

B. 2-(2,4-Dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title A compound, glycine-N-sulfonic acid 2,4-dimethoxybenzylamide (14.3 g, 47.0 mmol) is dissolved in 300 mL of THF, then HOBt (7.20 g, 47.0 mmol) is added as a solid and stirred until dissolved. EDCI (9.01 g, 47.0 mmol) is added as a solid and stirred for 10 minutes, followed by the addition of TEA (7.20 mL, 51.7 mmol). The reaction is stirred for 16 h, then evaporated on the rotary evaporator. The residue is partitioned between 1N aqueous HCl and EtOAc. The organic layer is dried over anhydrous $MgSO_4$. Filtration followed by evaporation gives an oil which solidifies on standing. This is dissolved in hot EtOAc and flash chromatographed on silica gel with 40% EtOAc in hexanes to afford 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid: $[M-1]^-$ = 285.

C. 4-[5-(2,4-Dimethoxybenzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]phenyl}-carbamic acid *t*-butyl ester

The title B compound, 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (98 mg, 0.34 mmol) and (4-hydroxymethylphenyl)carbamic acid t-butyl ester (153 mg, 0.68 mmol) and triphenylphosphine (180 mg, 0.68 mmol) are dissolved in THF (10 mL) in a small flask, with stirring under argon atmosphere. The reaction is cooled in an ice/water bath and diethylazodicarboxylate (0.107 mL, 0.68 mmol) dissolved in THF (0.107 mL) is added dropwise. After 16 h, the solvent is evaporated under reduced pressure and the residue is

taken up in a minimal amount of CH_2Cl_2 and chromatographed on silica gel with a gradient from 1% to 5% EtOAc in CH_2Cl_2 over 15 min to give {4-[5-(2,4-dimethoxybenzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-carbamic acid t-butyl ester as an oil: $[M+NH_4]^+$ = 509.

D. 5-(4-Aminobenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title C compound, {4-[5-(2,4-dimethoxybenzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]phenyl}carbamic acid t-butyl ester (20 mg, 0.041 mmol) is dissolved in CH_2Cl_2 (1 mL) followed by the addition of TFA (1 mL) in a 4 dram vial and sealed and stirred at RT overnight. Upon addition the reaction became light pink colored, progressing to deep purple after overnight. The rsolvent is evaporated under reduced pressure and the residue is taken up in 2 mL of MeCN/water (50/50). This is filtered through a 0.2 micron PTFE membrane filter and the filtrate collected. MeCN is removed under reduced pressure and water is removed by lyophilization 5-(4-amino-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one TFA salt as a yellow foam: $[M-1]^-$ = 240.

Example 10

The following examples are prepared analogously to Examples 8 and 9 using appropriately protected starting materials and standard reaction conditions.

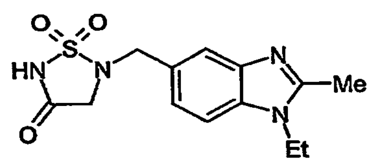
Example	Chemical Name	MS [m/z]
10-1	N-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-butyramide	$[M-1]^-$ = 310
10-2	1-Propyl-3-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-urea	$[M-1]^-$ = 325
10-3	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester	$[M-1]^-$ = 283
10-4	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid	$[M-1]^-$ = 269
10-5	2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid	$[M-1]^-$ = 269
10-6	5-(2-Methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 239
10-7	1,1-Dioxo-5-pyridin-3-ylmethyl-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 226
10-8	1,1-Dioxo-5-pyridin-2-ylmethyl-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 226
10-9	5-(6-Amino-pyridin-3-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 241
10-10	1,1-Dioxo-5-thiophen-2-ylmethyl-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 231

Example	Chemical Name	MS [m/z]
10-11	5-(4-Methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 255
10-12	5-(4-Amino-2-bromo-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 318
10-13	N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide	$[M-1]^-$ = 282
10-14	N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-methanesulfonamide	$[M-1]^-$ = 318
10-15	N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-methanesulfonamide	$[M-1]^-$ = 332
10-16	5-(4-Methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 239
10-17	Amino-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetic acid	$[M-1]^-$ = 298
10-18	2-Amino-N-propyl-2-[2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide	$[M-1]^-$ = 339
10-19	2-Amino-N-propyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide	$[M-1]^-$ = 339
10-20	2,2,2-Trifluoro-N-{propylcarbamoyl-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-methyl}-acetamide	$[M-1]^-$ = 435
10-21	2-Methanesulfonylamino-N-propyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide	$[M-1]^-$ = 417
10-22	2-Acetylamino-N-propyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-propionamide	$[M+H]^+$ = 397
10-23	2-Acetylamino-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-malonic acid diethyl ester	(mp = 197°C)
10-24	2-Amino-N-propyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-propionamide	$[M-1]^-$ = 353
10-25	2-Acetylamino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-propionic acid ethyl ester	$[M-1]^-$ = 382
10-26	Phenyl-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-acetic acid	$[M-1]^-$ = 269
10-27	1,1-Dioxo-5-phenethyl-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 239
10-28	5-[2-(4-Methyl-thiazol-5-yl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 260
10-29	5-[2-(3,4-Dimethoxy-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 299
10-30	5-[2-(2-Chloro-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 273
10-31	5-[2-(4-Amino-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 254

Example	Chemical Name	MS [m/z]
10-32	2,2,2-Trifluoro-N-{4-[2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-ethyl]-phenyl}-acetamide	$[M-1]^-$ = 350
10-33	N-{4-[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-ethyl]-phenyl}-butyramide	$[M-1]^-$ = 324
10-34	1,1-Dioxo-5-(2-pyridin-3-yl-ethyl)-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 240
10-35	1,1-Dioxo-5-(2-pyridin-4-yl-ethyl)-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 240
10-36	3-Phenyl-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-propionic acid	$[M-1]^-$ = 283
10-37	5-[2-(3-Amino-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 254
10-38	5-(4-Aminomethyl-naphthalen-1-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 304

Example 11

5-(1-Ethyl-2-methyl-1H-benzoimidazol-5-ylmethyl)-1,1-dioxo-1-1,2,5-thiadiazolidin-3-one



A. 4-Ethylamino-3-nitro-benzoic acid

To a suspension of 1.85 gm of 4-fluoro-3-nitrobenzoic acid (10 mmol) in 25 mL of MeOH is added 20 mL of ethylamine (2.0M in THF). The resulting yellow solution is stirred at 75°C for 5 h then at RT for 48h. The solvent is removed under reduced pressure, then water is added to the residue. The resulting orange suspension is acidified with 2N aqueous HCl and the yellow precipitate is collected by filtration, washed with water and dried in vacuo to give 4-ethylamino-3-nitro-benzoic acid: mp = 233-236°C; ^{1}H-NMR (DMSO-d_6) δ 12.83 (s, 1H), 8.61 (d, J = 1.84, 1H), 8.49 (m, 1H), 7.97 (dd, 1H), 7.12 (d, J = 9.2, 1H), 3.46 (m, 2H), 1.23 (t, 3H); $[M-1]^-$ = 209.

B. 3-Amino-4-ethylamino-benzoic acid

A solution of 1.56 gm (7.4 mmol) of the title A compound 4-ethylamino-3-nitro-benzoic acid in 60 mL of THF/ water (2:1) is hydrogenated at 20 psi over 300 mg of Raney nickel for 18 h. The catalyst is removed by filtration through Celite and the solvent is

removed under reduced pressure to give 3-amino-4-ethylamino-benzoic acid as a dark solid. This material is used as such in the next step.

C. 1-Ethyl-2-methyl-1H-benzoimidazole-5-carboxylic acid

A mixture of 1.4 gm (7.7 mmol) of the title B compound, 3-amino-4-ethylamino-benzoic acid and 15 mL (104 mmol) of triethyl orthoacetate in 20 mL of EtOH is refluxed for 7 h. The reaction mixture is allowed to cool to RT and the resulting suspension is filtered, washed with EtOH (2x) then methyl-t-butylether (MTBE, 1x) and dried in vacuo to give 1-ethyl-2-methyl-1H-benzoimidazole-5-carboxylic acid as a grey solid: mp >250°C; ^{1}H-NMR (DMSO-d_6) δ 12.65 (s, 1H), 8.11 (s, 1H), 7.82 (dd, 1H), 7.59 (d, J = 8.46, 1H), 4.26 (q, 2H), 2.57 (s, 3H), 1.30 (t, 3H); $[M-1]^-$ = 203.

D. 1-Ethyl-2-methyl-1H-benzoimidazole-5-carboxylic acid methyl ester

To a suspension of 1.1 gm (5.4 mmol) of the title C compound, 1-ethyl-2-methyl-1H-benzoimidazole-5-carboxylic acid in 25 mL of MeOH is added dropwise 0.7 gm (5.9 mmol) of thionyl chloride and the resulting solution is stirred at 70° for 6 h then at RT for 18 h. The solvent is removed under reduced pressure and 8% aqueous $NaHCO_3$ solution is added to the residue. The mixture is extracted with EtOAc (2x) and the organic phase is dried over anhydrous Na_2SO_4. The organic solution is concentrated until the product precipitated. The solid is collected by filtration, washed with EtOH (1x) and MTBE (1x) to give 1-ethyl-2-methyl-1H-benzoimidazole-5-carboxylic acid methyl ester as a beige solid: mp = 118-121°C; IR (KBr) 3430, 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.39 (s, 1H), 7.98 (dd, 1H), 7.32 (d, J = 8.45, 1H), 4.19 (q, 2H), 3.94 (s, 3H), 2.64 (s, 3H), 1.43 (t, 3H); $[M+1]^+$ = 219.

E. (1-Ethyl-2-methyl-1H-benzoimidazol-5-yl)-methanol

To a solution of 450 mg (2.06 mmol) of the title D compound, 1-ethyl-2-methyl-1H-benzoimidazole-5-carboxylic acid methyl ester in 5 mL of THF is added dropwise 2.1 mL (2.1 mmol) of lithium aluminum hydride (LAH, 1.0M in THF). The mixture is stirred at RT for 90 min, then saturated aqueous sodium sulfate solution is carefully added dropwise until a thick precipitate formed. MTBE is added to the mixture and the insoluble aluminum salts are removed by filtration through Celite. The solvent is removed under reduced pressure to give (1-ethyl-2-methyl-1H-benzoimidazol-5-yl)-methanol as an oil: ^{1}H-NMR ($CDCl_3$) δ 7.63 (s, 1H), 7.28 (m, 2H), 4.77 (s, 2H), 4.16 (q, 2H), 3.74 (t, broad, 1H), 2.60 (s, 3H), 1.40 (t, 3H); $[M+1]^+$ = 191.

F. 2-(2,4-Dimethoxy-benzyl)-5-(1-ethyl-2-methyl-1H-benzoimidazol-5-ylmethyl)-1,1-dioxo-1-1,2,5-thiadiazolidin-3-one

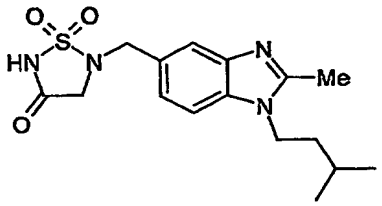
To a solution of 767 mg (2.7 mmol) of the title B compound in Example 9, 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one, 340 mg (1.8 mmol) of the title E compound, (1-ethyl-2-methyl-1H-benzoimidazol-5-yl)-methanol, and 545 mg (2.7 mmol) of tri-n-butyl-phosphine in 20 mL of THF (under argon) is added 460 mg (2.7 mmol) of N,N,N',N'-tetramethylazodicarboxamide (TMAD). The mixture is stirred at RT for 24 h after which time the resulting precipitate is filtered and washed with a small volume of THF. The filtrate is evaporated to give an oil which is flash chromatographed using 5% EtOH/EtOAc to afford 2-(2,4-dimethoxy-benzyl)-5-(1-ethyl-2-methyl-1H-benzoimidazol-5-ylmethyl)-1,1-dioxo-1-1,2,5-thiadiazolidin-3-one as a solid: ^{1}H-NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.31-7.20 (m, 3H), 6.46 (m, 2H), 4.79 (s, 2H), 4.44 (s, 2H), 4.17 (q, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.73 (s, 2H), 2.61 (s, 3H), 1.41 (t, 3H); $[M+1]^+$ = 459.

G. 5-(1-Ethyl-2-methyl-1H-benzoimidazol-5-ylmethyl)-1,1-dioxo-1-1,2,5-thiadiazolidin-3-one

A solution of 200 mg (0.44 mmol) of the title F compound, 2-(2,4-dimethoxy-benzyl)-5-(1-ethyl-2-methyl-1H-benzoimidazol-5-ylmethyl)-1,1-dioxo-1-1,2,5-thiadiazolidin-3-one in 4 mL of TFA/CH_2Cl_2 (1:1) is stirred at RT for 90 min. The solvent is removed from the purple solution and 4 mL of MeCN/water (1:1) is added. After stirring the mixture for 30 min, the mixture is centrifuged and the supernatant is decanted. The solvent is removed under reduced pressure and the residue is chromatographed by preparative HPLC (gradient: 10% MeCN/water → 100% MeCN, each containing 0.1% TFA). The proper fractions are combined and lyophylized to give 5-(1-ethyl-2-methyl-1H-benzoimidazol-5-ylmethyl)-1,1-dioxo-1-1,2,5-thiadiazolidin-3-one TFA salt as an amorphous solid: mp = 255-265°C; ^{1}H-NMR (DMSO-d_6) δ 7.91 (d, J = 8.29, 1H), 7.77 (s, 1H), 7.56 (d, J = 8.67, 1H), 4.44 (q, 2H), 4.27 (s, 2H), 3.47 (s, 2H), 2.82 (s, 3H), 1.39 (t, 3H); $[M-1]^-$ = 307.

Example 12

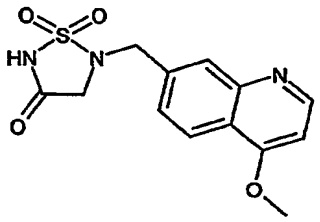
5-[2-Methyl-1-(3-methyl-butyl)-1H-benzoimidazol-5-ylmethyl]-1,1-dioxo-1-1,2,5-thiadiazolidin-3-one



The title compound is prepared analogously to Example 11: mp = 70-75°C; ^{1}H-NMR (DMSO-d_6) δ 7.91 (d, J = 8.46, 1H), 7.78 (s, 1H), 7.57 (dd, 1H), 4.40 (m, 2H), 4.33 (s, 2H), 3.63 (s, 2H), 2.83 (s, 3H), 1.78-1.60 (m, 3H), 0.98 (d, J = 5.88, 6H); $[M-1]^-$ = 349.

Example 13

5-(4-Methoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one



A. 4-Chloro-7-trifluoromethylquinoline

1.0 g (4.32 mmols) of 4-chloro-7-trifluoromethylquinoline in 20 mL of 80% sulfuric acid in a sealed tube is heated to 200°C for 18 h. The tube is cooled to RT, vented, and poured into 200 mL water, which is made basic with sodium hydroxide to pH 3-4. The resulting solid is filtered and washed with water, then dissolved in 100 mL 1N aqueous NaOH, filtered to remove insolubles, and extracted with EtOAc. The aqueous solution is acidified with 1N aqueous HCl to pH 3-4, filtered, and the collected solid washed with water. The solid is dried to give 4-chloro-7-trifluoromethylquinoline: ^{1}H-NMR (DMSO-d_6) δ 7.90 (1H, d, J = 4.8), 8.22 (1H, dd, J = 8.7, 1.5), 8.32 (1H, d, J = 8.7), 8.63 (1H, d, J = 1.5), 8.96 (1H, d, J = 4.8), 13.7 (1H, br).

B. 7-Carbomethoxy-4-methoxyquinoline

606 mg (2.92 mmol) of the title A compound, 4-chloro-7-quinoline carboxylic acid in 50 mL MeOH is saturated with HCl gas, then heated at 60°C for 18 h. The solvent is removed on a rotary evaporator, and the residue taken up in water, made basic with $NaHCO_3$, and extracted twice with EtOAc. Combined organic fractions are dried over anhydrous $MgSO_4$, filtered, and the solvent is removed to afford the crude product. This is chromatographed on a Biotage 40M column with 98:2 EtOAc/EtOH to give 7-carbomethoxy-4-methoxyquinoline: mp = 147-148°C; ^{1}H-NMR ($CDCl_3$) δ 4.00 (3H, s), 4.08 (3H, s), 6.81 (1H, d, J = 5.2), 8.10 (1H, dd, J = 8.7, 1.5), 8.26 (1H, d, J = 8.7), 8.75 (1H, d, J = 1.5), 8.83 (1H, d, J = 5.2); $[M+1]^+$ = 218.

C. (4-Methoxy-quinolin-7-yl)-methanol

A solution of 2 mL of 1 M LAH (2 mmol) in 25 mL THF is cooled in an ice bath. 450 mg (2.07 mmol) of the title B compound, 7-carbomethoxy-4-methoxyquinoline suspended in 15 mL THF is added and allowed to stir at RT for 18 h. The mixture is quenched with saturated aqueous Na_2SO_4, filtered, and the filtrate dried over anhydrous $MgSO_4$, filtered, and solvent removed to give (4-methoxyquinolin-7-yl)-methanol: ^{1}H-NMR ($CDCl_3$) δ 4.04 (3H, s), 4.89 (2H, s), 6.72 (1H, d, J = 5.3), 7.51 (1H, d, J = 8.5), 8.04 (1H, s), 8.16 (1H, d, J = 8.5), 8.72 (1H, d, J = 5.3).

D. 2-(2,4-Dimethoxy-benzyl)-5-(4-methoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

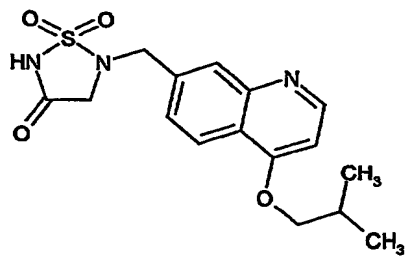
745 mg (2.60 mmol) of the title B compound in Example 9, 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one, 328 mg (1.73 mmol) of the title E compound, (4-methoxyquinoline-7-yl)-methanol and 448 mg (526 mg., 2.60 mmol) of tributylphosphine are stirred in 5 mL of THF. 448 mg (2.60 mmols) of TMAD is added and the mixture is stirred for 18 h. A spatula tip of Raney nickel is added, the mixture is stirred for 10 min, and then filtered through Celite. The filtrate is evaporated to dryness and chromatographed on a Biotage 40M column with 98:2 EtOAc/EtOH to afford 2-(2,4-dimethoxy-benzyl)-5-(4-methoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one: mp = 128-132°C; ^{1}H-NMR ($CDCl_3$) δ 3.79 (2H, s), 3.81 (3H, s), 3.85 (3H, s), 4.06 (3H, s), 4.51 (2H, s), 4.82 (2H, s), 6.46 (2H, m), 6.78 (1H, d, J = 5.2) 7.30 (1H, m), 7.53 (1H, dd, J = 8.5, 1.5), 7.96 (1H, s), 8.22 (1H, d J = 8.5), 8.77 (1H, d, J = 5.2); $[M+1]^+$ = 458.

E. 5-(4-Methoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

210 mg (459 μmol) of the title D compound, 2-(2,4-dimethoxy-benzyl)-5-(4-methoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one is stirred for 30 min in 4 mL of 1:1 TFA/CH_2Cl_2. The solvent is removed on a rotary evaporator and the residue triturated with 4 mL of 1:1 MeCN/water. This mixture is filtered through a 0.2 micron disk and the solvent is removed. The resulting material is purified by preparative LC/MS, and the collected product fractions are lyophilized to give 5-(4-methoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one: $[M-1]^-$ = 306.

Example 14

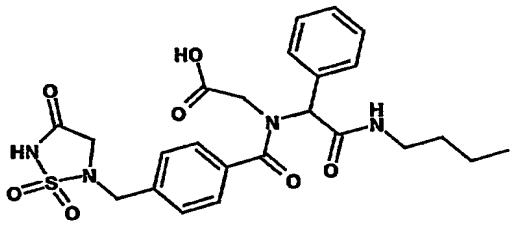
5-(4-Isobutoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one



The title compound is prepared analogously to Example 13: ^{1}H-NMR (DMSO-d_6) δ1.10 (3H, d, J = 6.6), 2.27 (1H, m, J = 6.6), 3.66 (2H, s), 4.34 (2H, d, J = 6.6), 4.46 (2H, s), 7.55 (1H, d, J = 6.8), 7.86 (1H, dd, J = 8.6, 1.1), 8.14 (1H, s), 8.37 (1H, d, J = 8.6), 9.15 (1H, d, J = 6.8); $[M+1]^+$ = 350, $[M-1]^-$ = 348.

Example 15

N-(Butylcarbamoyl-phenyl-methyl)-N-(4-(1,1,4-trioxo-1,2,5-thiazodiazolidin-2-ylmethyl)-benzoyl)-amino-acetic acid.



A. 4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid

To a suspension of the title B compound in Example 9, 2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (13,87 g, 48.4 mmol) and 4-bromomethylbenzoic acid (10.42 g, 48.4 mmol) in CH_2Cl_2 (150 mL) is added DBU (14.5 mL, 96.9 mmol) at once and the mixture is stirred at RT overnight. The reaction mixture is washed two times with 1N aqueous HCl, one time with aqueous saturated NaCl, then dried over anhydrous $MgSO_4$ and concentrated to a small volume to crystallize the product. The solid is collected by filtration, washed with ethyl ether and dried under high vacuum to afford 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid: mp = 175-177^{0}C; $[M-1]^-$ = 419.

B. N-(Butylcarbamoyl-phenylmethyl)-N-(4-(1,1,4-trioxo-1,2,5-thiazodiazolidin-2-ylmethyl)-benzoyl)-amino-acetic acid

Wang resin (100-200 mesh, 1,11 mmol/g substitution, 3.41 g, 3.78 mmol) is suspended in pyridine (25 mL) and the mixture is shaken for 15 min and drained. The resin is resuspended in pyridine (30 mL), Fmoc-glycine (4.5 g, 15.1 mmol), 4-dimethylamino-

pyridine (DMAP, 46 mg, 0.378 mmol) and N,N'-dicyclohexylcarbonylcarbodiimide (3.12 g, 15.1 mmol) are added and the mixture is shaken overnight. The resin is drained and washed successively with DMF (20 mL, 3 times), MeOH (20 mL, 2 times), THF (20 mL, 1 time) and alternatively with CH_2Cl_2 (20 mL, 3 times) and MeOH (20 mL, 2 times). The resin is dried under high vacuum overnight. The dry Wang resin-Fmoc-glycine ester (140 mg, 0.106 mmol) is treated with 20% piperidine in CH_2Cl_2 (3 mL, 15 min, 2 times) and washed alternatively with CH_2Cl_2 (3 mL, 2 times) and MeOH (3 mL, 2 times) and again with CH_2Cl_2 (3 mL, 2 times). The resin is then suspended in CH_2Cl_2-MeOH (1:1, 4 mL), and the title A compound, 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid (133 mg, 0.317 mmol), benzaldehyde (32 µl, 0.317 mmol) and butylisonitrile (33 µl, 0.317 mmol) are added and the mixture is shaken for 48 h. The resin is drained and is washed alternatively with CH_2Cl_2 (4 mL, 2 times), MeOH (4 mL, 2 times) and again with CH_2Cl_2 (4 mL, 2 times). The resin is then shaken with CH_2Cl_2-TFA (1:1, 4 mL) for 4 h and drained into a receiving flask. The resin is washed with CH_2Cl_2-TFA (1:1, 4 mL) and drained into the same receiving flask. The solvents are evaporated to dryness under a stream of nitrogen and the residue is further dried under high vacuum. The residue is purified using a Micromass LC/MS system (Phenominex Luna 5µ, 60x21.2 mm C-8 column, 5 to 100 gradient over 8 min, A = water/0.1% TFA, B = MeCN/0.1% TFA, 20mL/min flow rate). The fractions containing the product are pooled and evaporated to a small volume which is subsequently lyophilized to give N-(butylcarbamoyl-phenyl-methyl)-N-(4-(1,1,4-trioxo-1,2,5-thiazodiazolidin-2-ylmethyl)-benzoyl)-amino-acetic acid as a foam: $[M-1]^-$ = 515.

Example 16

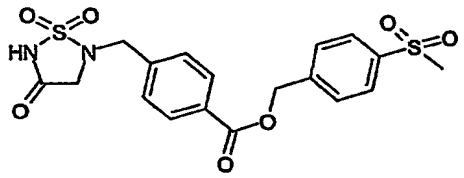
The following examples are prepared analogously to Example 15 by replacing benzaldehyde with the appropriate aldehyde as a starting material.

Example	Chemical Name	MS [m/z]
16-1	{[Butylcarbamoyl-(4-ethyl-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid	$[M-1]^-$ = 543
16-2	{[Butylcarbamoyl-(3-phenoxy-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid	$[M-1]^-$ = 607
16-3	{[Butylcarbamoyl-(4-methoxy-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid	$[M-1]^-$ = 545
16-4	{[(2-Bromo-phenyl)-butylcarbamoyl-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid	$[M-1]^-$ = 593, 595

Example	Chemical Name	MS [m/z]
16-5	{(Butylcarbamoyl-naphthalen-2-yl-methyl)-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid	$[M-1]^-$ = 565
16-6	{[Butylcarbamoyl-(4-chloro-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid	$[M-1]^-$ = 549, 551
16-7	{[(3-Benzyloxy-phenyl)-butylcarbamoyl-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid	$[M-1]^-$ = 621
16-8	{((E)-1-Butylcarbamoyl-3-phenyl-allyl)-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid	$[M-1]^-$ = 541
16-9	N-(1-Butylcarbamoyl-3-phenyl-propyl)-N-(4-(1,1,4-trioxo-1,2,5-thiazodiazolidin-2-ylmethyl)-benzoyl)-amino-acetic acid	$[M-1]^-$ = 543

Example 17

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methanesulfonyl-benzyl ester



A. 4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid

To a suspension of the title B compound in Example 9, 2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one, (13,87 g, 48.4 mmol) and 4-bromomethylbenzoic acid (10.42 g, 48.4 mmol) in CH_2Cl_2 (150 mL), DBU (14.5 mL, 96.9 mmol) is added at once and the mixture is stirred at RT overnight. The reaction mixture is washed two times with 1N aqueous HCl, one time with saturated aqueous NaCl, then dried over anhydrous $MgSO_4$ and evaporated to a small volume to crystallize the product. The solid is collected by filtration, washed with ethyl ether and dried under high vacuum to afford 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid: mp = 175-177°C; $[M-1]^-$ = 419.

B. 4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoyl chloride

1.66 g (3.47 mmols) of the title A compound, 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid and 2.5 mL (34 mmol) of SOCl2 in 40 mL toluene are heated at 110°C until only a small amount of dark solid remained undissolved. The solution is filtered and the solvent is removed on a rotary evaporator and the residual

dark purple solid is dried in a vacuum oven overnight to give 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoyl chloride which is used as such without further purification.

C. 4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid 4-methylsulfanyl-benzyl ester

400 mg (911 μmol) of the title B compound, 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoyl chloride, 140 μL (1.0 mmol) of TEA and 141 mg (914 μmol) of 4-(methylthio)benzyl alcohol in 10 mL of CH_2Cl_2 are stirred at RT for 18 h. The solvent is removed under reduced pressure and the residue is chromatographed on a Biotage 40M column with 98/2 - CH_2Cl_2/EtOAc to give 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid 4-methylsulfanyl-benzyl ester: $[M+NH_4]^+$ = 574.

D. 4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid 4-methanesulfonyl-benzyl ester

150 mg (270 μmol) of the title C compound, 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid 4-methylsulfanyl-benzyl ester and 181 mg (810 μmols) of 81% m-chloroperbenzoic acid are stirred overnight in 10 mL CH_2Cl_2. The solution is extracted with aqueous NaHCO3, then dried, filtered, and solvent removed to afford 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid 4-methanesulfonyl-benzyl ester: $[M+NH_4]^+$ = 606.

E. 4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methanesulfonyl-benzyl ester

90 mg (150 μmol) of the title D compound, 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid 4-methanesulfonyl-benzyl ester is stirred in 4 mL of 1:1 - TFA:CH_2Cl_2 for 50 min. The solvent is removed and the residue triturated with 4 mL of 1:1 - MeCN:H_2O. This mixture is filtered through a 0.2 μ disk and the solvent is removed. The resulting material is purified by LC/MS and afforded 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methanesulfonyl-benzyl ester: ^{1}H-NMR (DMSO-d_6) δ 3.22 (3H, s), 3.71 (2H, s), 4.27 (2H, s), 5.48 (2H, s), 7.54 (2H, d, J = 8.1), 7.74 (2H, d, J = 8.1), 7.96 (2H, d, J = 8.5), 8.01 (2H, J = 8.5); $[M-1]^-$ = 437.

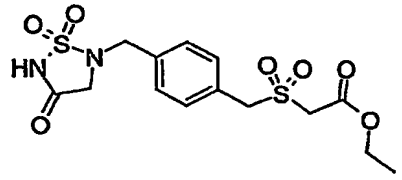
Example 18

The following compounds are prepared analogously to Example 17 by replacing 4-(methylthio)benzyl alcohol with the appropriate alcohol as a starting material.

Example	Chemical Name	MS [m/z]
18-1	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-chloro-benzyl ester	$[M-1]^-$ = 393
18-2	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-butyl-benzyl ester	$[M-1]^-$ = 415
18-3	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-hydroxymethyl-benzyl ester	$[M-1]^-$ = 389
18-4	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-phenethyl-benzyl ester	$[M-1]^-$ = 463
18-5	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid biphenyl-2-ylmethyl ester	$[M-1]^-$ = 435
18-6	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-difluoromethoxy-benzyl ester	$[M-1]^-$ = 424
18-7	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-(carboxy-difluoro-methyl)-thiophen-2-ylmethyl ester	$[M-1]^-$ = 459

Example 19

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenylmethanesulfonyl]-acetic acid ethyl ester



A. 5-(4-Bromomethyl-benzyl)-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

A solution of the title B compound in Example 9, 2,4-dimethoxybenzyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one (2.0 g, 6.98 mmol) in CH_2Cl_2 (100 mL) is treated with DBU (1.06 g, 6.98 mmol). α, α'-Dibromo-p-xylene (9.2 g, 34.9 mmol) is added and the mixture is stirred at RT for 16 h. The mixture is filtered and the solvent volume is reduced to 20 mL. The mixture is chromatographed on silica gel using CH_2Cl_2 as the eluent. The residual α, α'-dibromo-p-xylene is removed from the product by triturating with Et_2O to afford 5-(4-bromomethyl-

benzyl)-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid: $[M+H]^+ = 469$.

B. {4-[5-(2,4-Dimethoxybenzyl)-1,1,4-trioxo-1-1,2,5-thiadiazolidin-2-ylmethyl]-benzylsulfanyl}-acetic acid ethyl ester

A solution of the title A compound, 5-(4-bromomethyl-benzyl)-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (200 mg, 0.43 mmol) in nitrogen degassed DMF (8 mL) is treated with Cs_2CO_3 (278 mg, 0.85 mmol) and mercaptoacetic acid ethyl ester (51 mg, 0.43 mmol). The mixture is stirred at RT for 16 h. The mixture is partitioned between EtOAc and water, and the organic layer is washed with water (3X) and dried over anhydrous $MgSO_4$. The solvent is evaporated and the residue is chromatographed on silica gel using 10% → 100% EtOAc in hexanes as the eluent to afford {4-[5-(2,4-dimethoxybenzyl)-1,1,4-trioxo-1-1,2,5-thiadiazolidin-2-ylmethyl]-benzylsulfanyl}-acetic acid ethyl ester as a white solid.

C. {4-[5-(2,4-Dimethoxybenzyl)-1,1,4-trioxo-1-1,2,5-thiadiazolidin-2-ylmethyl]-phenylmethanesulfonyl}-acetic acid ethyl ester

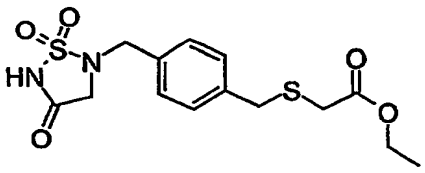
A solution of the title B compound, {4-[5-(2,4-dimethoxybenzyl)-1,1,4-trioxo-1-1,2,5-thiadiazolidin-2-ylmethyl]-benzylsulfanyl}-acetic acid ethyl ester (55 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) is treated with 3-chloroperoxybenzoic acid (47 mg, 0.27 mmol). The mixture is stirred at RT for 4 h and then washed with saturated aqueous $NaHCO_3$ solution. The organic layer is dried over anhydrous $MgSO_4$, and the solvent is evaporated to afford {4-[5-(2,4-dimethoxybenzyl)-1,1,4-trioxo-1-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl-methanesulfonyl}-acetic acid ethyl ester: $[M-H]^- = 539$.

D. [4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenylmethanesulfonyl]-acetic acid ethyl ester

A solution of the title C compound, {4-[5-(2,4-dimethoxybenzyl)-1,1,4-trioxo-1-1,2,5-thiadiazolidin-2-ylmethyl]-phenylmethanesulfonyl}-acetic acid ethyl ester (60 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) is treated with TFA (2 mL). The mixture is stirred at RT for 16 h, and the volatiles are evaporated. The residue is stirred in MeCN/water (1:1, 6 mL) for 30 min. The mixture is passed through a 0.2μ Acrodisc and the solvents are evaporated. The residue is purified via LC/MS to afford [4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenylmethane-sulfonyl]-acetic acid ethyl ester as a white solid: $[M-H]^- = 389$.

Example 20

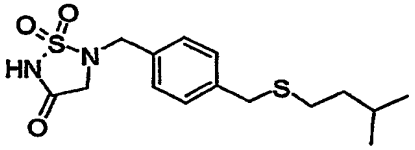
[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylsulfanyl]-acetic acid ethyl ester



The title compound is prepared by treating the title B compound in Example 19 with TFA using conditions described in Example 19: $[M-1]^-$ = 357.

Example 21

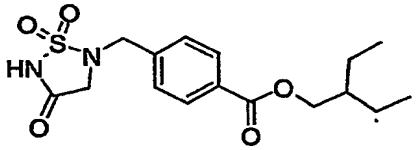
5-[4-(3-Methyl-butylsulfanylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one



The title compound is prepared analogously to Example 19: $[M-1]^-$ = 341.

Example 22

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-ethyl-butyl ester



A. 4-Bromomethyl-benzoyl chloride

A solution of 4-bromomethyl-benzoic acid (8.6 g, 0.04 mol) in 7.23 mL $SOCl_2$ (0.1 mol) is heated to reflux for 5 h. $SOCl_2$ is removed under reduced pressure, and the residue is recrystalized from hexane to afford 4-bromomethyl-benzoyl chloride as a white crystalline solid.

B. 4-Bromomethyl-benzoic acid 2-ethyl-butyl ester

A solution of the title A compound, 4-bromomethyl-benzoyl chloride (466 mg, 2 mmol) in 3mL CH_2Cl_2 is added dropwise to a cooled solution of 2-ethyl-1-butanol (204 mg, 2 mmol) and TEA (202 mg, 2 mmol) in 10 mL CH_2Cl_2 chloride at 0~5°C (ice bath) over a period of 30 min. After the addition is completed, the reaction mixture is allowed to warm to RT and stirred overnight. The solvent is evaporated and the residue is partitioned between hexane and water. The organic phase is separated and dried over anhydrous $MgSO_4$ and

A. Glycine-N-sulfonic acid 4-methoxybenzylamide

Glycine methyl ester-N-sulfonic acid 4-methoxybenzylamide (3.03 g, 10.5 mmol, prepared analogously to literature procedure as described by Ducry, L.; Reinelt, S.; Seiler, P.; Diederich, F. *Helvetica Chimica. Acta.* **1999**, *82*, 2432-47) is dissolved in 80 mL of 1,4-dioxane, then added 20 mL of water, followed by 21 mL of 1N aqueous NaOH solution. After 40 min, 1,4-dioxane is evaporated on the rotary evaporator, and the remaining aqueous solution is extracted with Et_2O. The aqueous solution is acidified with 1N aqueous HCl solution and extracted with EtOAc. The organic layer is dried over anhydrous Na_2SO_4, filtered and evaporated to dryness to give glycine-N-sulfonic acid 4-methoxybenzylamide: $[M-1]^-$ = 273.

B. 2-(4-Methoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title A compound, glycine-N-sulfonic acid 4-methoxybenzylamide (2.51 g, 9.2 mmol) is dissolved in 160 mL of THF, then HOBt (1.41 g, 9.2 mmol) is added as a solid and stirred until dissolved. EDCI (1.76 g, 9.2 mmol) is added as a solid and stirred for 10 min, followed by the addition of TEA (1.42 mL, 10.2 mmol). The reaction is stirred for 16 h, then evaporated down on the rotary evaporator. The residue is partitioned between 1N aqueous HCl solution and EtOAc. The organic layer is washed with saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gives an oil which solidifies on standing. This is dissolved in hot EtOAc, concentrated down to 20 mL, filtered to remove solids and flash chromatographed on silica gel using 40% EtOAc in hexanes as the eluent to afford 2-(4-methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid: mp = 111-113°C; $[M-1]^-$ = 255.

C. 5-(3-Iodo-benzyl)-2-(4-methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title B compound, 2-(4-methoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (1.02 g, 3.98 mmol), 3-iodo-benzyl alcohol (1.01 mL, 7.95 mmol) and triphenylphosphine (2.10 g, 8.0 mmol) are dissolved in THF (50 mL) and the flask is cooled to 5°C. Diethylazodicarboxylate (1.26 mL, 8.0 mmol) is dissolved in THF (10 mL) and added by pipette to the stirred cooled solution above, and allowed to stir with gradual warming to RT over 16 h. The reaction mixture is concentrated on a rotary evaporator to yield a yellow oil. This is chromatographed on a 110 g silica gel RediSep column (Isco, Inc.) with a 30 mL/min gradient elution of 0:100 (EtOAc:CH_2Cl_2) to 5:95 over 25 min. Fractions containing product are combined and concentrated to yield an oil, which spontaneously crystalizes. This is triturated with Et_2O to yield 5-(3-iodo-benzyl)-2-(4-methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid: mp = 98-100°C.

D. (S)-2-tert-Butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-propionic acid benzyl ester

Zinc foil (99.9% Aldrich 35,602-6, 145 mg, 2.22 mmol) is cut in small pieces and put in a heat dried 1 dram vial with septum cap under argon balloon. Added DMF (freshly distilled from CaH_2 under argon, 0.4 mL) and then 1,2-dibromoethane (0.007 mL, 0.08 mmol), and heated in a 50°C water bath for 10 min. Let cool 5 min, then added trimethylsilyl chloride (0.004 mL, 0.032 mmol) and let stir 25 min. (R)-2-tert-Butoxycarbonylamino-3-iodo-propionic acid benzyl ester (Fluka, 417 mg, 1.03 mmol) is then dissolved in DMF (1 mL) and added to the stirred Zinc mixture by syringe. This is allowed to stir for 1h. The title C compound, 5-(3-iodo-benzyl)-2-(4-methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (378 mg, 0.80 mmol), tri-o-tolylphosphine (49 mg, 0.16 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (37 mg, 0.04 mmol) are added as solids to a separate heat dried 20 mL septum capped vial under argon balloon. Rapidly added DMF (2 mL) to this, and then decanted off the zinc reagent formed in the previous vessel from the unreacted zinc, and added it to the Pd catalyst containing mixture. After 1.5 h, the resulting reaction mixture is poured water (100 mL). Extracted with EtOAc (2 x 100 mL). Washed combined EtOAc layers with water (1 x 200 mL) and saturated aqueous NaCl solution (1 x 200 mL). Dried over anhydrous $MgSO_4$, filtered and concentrated to get a yellow oil. This is chromatographed on a 35 g silica gel RediSep column (Isco, Inc.) with a 30 mL/min gradient elution of 15:85 (EtOAc:hexane) to 60:40 over 20 min. Fractions containing product are combined and concentrated to yield (S)-2-tert-butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-propionic acid benzyl ester as a light brown foam: $[M+1]^+ = 624$.

E. (S)-2-tert-Butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-propionic acid

The title D compound, (S)-2-tert-butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-propionic acid benzyl ester (127 mg, 0.20 mmol) is dissolved in EtOAc/EtOH (50:50) (56 mL) and 10% palladium on carbon (35 mg) is added, then the mixture treated with 45 psi of hydrogen on a Parr shaker apparatus. After two 90 min runs, starting material is not completely consumed, so another aliquot of 10% palladium on carbon (35 mg) is added and after shaking at 45 psi hydrogen for 30 min, the reaction is complete. The reaction mixture is filtered through celite and concentrated, then pumping under high vacuum to give (S)-2-tert-butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-propionic acid as a

white foam: $[M+1]^+$ =534.

F. ((S)-2-{3-[5-(4-Methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-1-pentylcarbamoyl-ethyl)-carbamic acid tert-butyl ester

HOBt (28 mg, 0.179 mmol), pentyl amine (0.021 mL, 0.179 mmol) and EDCI (38 mg, 0.198 mmol) are added to a solution of the title E compound, (S)-2-tert-butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-propionic acid (96 mg, 0.179 mmol) in CH_2Cl_2 (4 mL) and this is stirred at RT for 2h. The reaction is then concentrated on the rotovap and taken up in EtOAc which is successively washed with 1N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution 3x and then with saturated aqueous NaCl. It is then dried over anhydrous $MgSO_4$, filtered and concentrated to yield the product as an oil. This is chromatographed on a 10 g silica gel RediSep column (Isco, Inc.) with a 30 mL/min gradient elution of 30:70 (EtOAc:hexane) to 60:40 over 10 min. Fractions containing product are combined and concentrated to yield ((S)-2-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-1-pentylcarbamoyl-ethyl)-carbamic acid tert-butyl ester as a white foam: $[M+1]^+$ = 603.

G. (S)-2-Amino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-N-pentyl-propionamide

The title G compound, ((S)-2-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-1-pentylcarbamoyl-ethyl)-carbamic acid tert-butyl ester (77 mg, 0.127 mmol) is dissolved in CH_2Cl_2 (1 mL), then added TFA (1 mL) and stirred. After 30 min, the solvent is evaporated under stream of nitrogen. The residue is partitioned between EtOAc and saturated aqueous $NaHCO_3$, then saturated aqueous NaCl, then the EtOAc layer is dried over $MgSO_4$, filtered and concentrated to yield (S)-2-amino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-N-pentyl-propionamide as a clear oil: $[M+1]^+$ = 503.

H. (S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-N-pentyl-propionamide

HOBt (19 mg, 0.125 mmol), (S)-2-acetylamino-3-phenyl-propionic acid (26 mg, 0.125 mmol) and EDCI (26 mg, 0.138 mmol) are added to a solution of the title G compound, (S)-2-amino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-N-pentyl-propionamide (63 mg, 0.125 mmol) in CH_2Cl_2 (4 mL) and this is stirred at RT for 30 min. The reaction is then concentrated on the rotovap and taken up in EtOAc which is successively washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$ solution 3x and

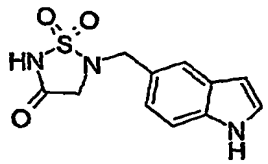
then saturated aqueous NaCl. It is then dried over anhydrous $MgSO_4$, filtered and concentrated to yield (S)-2-((S)-2-acetylamino-3-phenyl-propionylamino)-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-N-pentyl-propionamide as a white foam: $[M+1]^+ = 692$.

I. (S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-ethyl}-3-phenyl-propionamide

The title H compound, (S)-2-((S)-2-acetylamino-3-phenyl-propionylamino)-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-phenyl}-N-pentyl-propionamide (77 mg, 0.111 mmol) is dissolved in TFA (2.2 mL) containing tert-butyl-dimethylsilane (0.055 mL, 0.33 mmol) and heated at 80°C for 3.75 h. Then the reaction is concentrated under nitrogen stream to give a tan solid. This is taken up in 60% MeCN:water, then water (1 mL) is added, and the mixture filtered through a 0.1 micron Acrodisc filter. The resulting mixture is loaded onto a preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D., particle size S-5 micron, 12 nM) in 7 aliquots and eluted at 30 mL/min with a gradient of 90:10 (water containing 0.1% TFA: MeCN) at 0 min to 10:90 at 5 min. Then held at 10:90 until 7 min. Fractions containing product are combined and concentrated on a Savant Speedvac to yield the product as a white foam which still contained an unknown impurity by HPLC. This is chromatographed again, using the same column, but a different elution gradient, 90:10 (water containing 0.1% TFA: MeCN) at 0 min to 40:60 at 14 min. Fractions containing product are combined and concentrated to yield (S)-2-acetylamino-N-{(S)-1-pentylcarbamoyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-ethyl}-3-phenyl-propionamide as a white film: $[M+1]^+ = 572$.

Example 25

5-(1H-Indol-5-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one



A. N-(2-Trimethylsilanyl-ethoxycarbonyl-aminosulfonyl)-N-(1H-indol-5ylmethyl)-glycine methyl ester.

Chlorosulfonylisocyanate (0.082 mL, 0.95 mmol) is added to CH_2Cl_2 (6 mL) in a dry round bottomed flask under argon balloon, and cooled with stirring in an ice/salt/water bath. Trimethylsilylethanol (0.137 mL, 0.96 mmol) in CH_2Cl_2 (1 mL) is added to this solution and

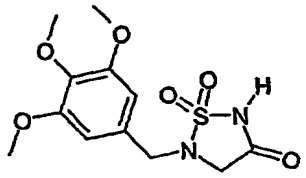
stirred while maintaining the cooling for 1h. Then a solution [(1H-Indol-5-ylmethyl)-amino]-acetic acid methyl ester (167 mg, 0.77 mmol, obtained by alkylation of C-(1H-Indol-5-yl)-methylamine using the method of Tohru Fukuyama et. al., Tett. Lett. 38 (33) pp. 5831-34, 1997) and TEA (0.41 mL, 2.9 mmol) in CH_2Cl_2 (6 mL) is added into this above mentioned stirred, cooled solution. After 1h, the reaction is poured into 40 mL of 1N aqueous HCl and extracted with Et_2O. The ether layer is washed with 1N aqueous HCl, separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The resulting residue is chromatographed on a 10 g silica gel RediSep (Isco Inc.) column with a 30 mL/min gradient elution of 15:85 (EtOAc:hexane) to 40:60 over 15 min. Fractions containing product are combined and evaporated yield N-(2-trimethylsilanyl-ethoxycarbonyl-aminosulfonyl)-N-(1H-indol-5ylmethyl)-glycine methyl ester as a yellow oil: ^{1}H-NMR (300MHz, DMSO-d_6) δ 0.0 (s, 9H), 0.9 (t, 2H), 3.55 (s, 3H), 3.9 (s, 2H), 4.05 (t, 2H), 4.5 (s, 2H), 6.4 (s, 1H), 6.95 (d, 1H), 7.3 (m, 2H), 7.4 (s, 1H), 12.0 (s, 1H), 12.4 (s, 1H).

B. 5-(1H-Indol-5-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

Tetrabutylammonium fluoride trihydrate (252 mg, 0.80 mmol) and AcOH (0.057 mL, 1.0 mmol) are dissolved in tetrahydrofuran (4 mL) and this is used to dissolve the title A compound, N-(2-trimethylsilanyl-ethoxycarbonyl-aminosulfonyl)-N-(1H-indol-5ylmethyl)-glycine methyl ester (90 mg, 0.20 mmol) in a thick-walled round bottomed flask. This is sealed and stirred in an oil bath at 80°C for 16 h. The reaction is allowed to cool, then diluted with 1N aqueous HCl (5 mL) and Et_2O (25 mL). The organic layer is separated and washed with water (2 x 5 mL) and saturated aqueous NaCl (5 mL), then separated, dried over anhydrous $MgSO_4$, filtered and evaporated, to yield the crude product as a brown oil. This is taken up in water (4.5 mL), MeCN (0.7 mL) and DMSO (1 mL). The resulting mixture is loaded onto a preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D., particle size S-5 micron, 12 nM) in 3 aliquots and eluted at 30 mL/min with a gradient of 90:10 (water containing 0.1% TFA: MeCN) at 0 min to 10:90 at 5 min. Then held at 10:90 until 7 minutes. Fractions containing product are combined and concentrated on a Savant Speedvac to yield 5-(1H-indol-5-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a light tan foam: $[M-1]^-$ = 264.

Example 26

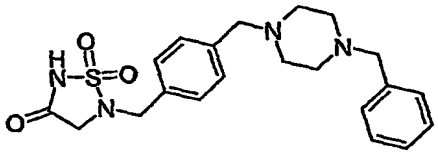
1,1-Dioxo-5-(3,4,5-trimethoxy-benzyl)-1,2,5-thiadiazolidin-3-one



The title compound is prepared analogously to Example 25 using 3,4,5-trimethoxybenzylamine as the starting material: $[M-1]^-$ = 315.

Example 27

5-[4-(4-Benzyl-piperazin-1-ylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one



A. 4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1-1,2,5-thiadiazolidin-2-ylmethyl]-benzaldehyde

DBU (4.36g, 0.0286 mol) is added to a suspension of 4-bromomethyl-benzaldehyde (5.70 g, 0.0286 mol) and the title B compound in Example 9, 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (8.2 g, 0.0286 mol) in CH_2Cl_2 (100mL) slowly at RT. After the addition is completed, the resulting solution is stirred overnight. The solvent is evaporated under reduced pressure and the residue is flash chromatographed on silica gel with CH_2Cl_2/EtOAc (gradient 5~25%) to afford 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1-1,2,5-thiadiazolidin-2-ylmethyl]-benzaldehyde as a white solid.

B. 5-[4-(4-Benzyl-piperazin-1-ylmethyl)-benzyl]-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

A mixture of the title A compound, 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1-1,2,5-thiadiazolidin-2-ylmethyl]-benzaldehyde (202 mg, 0.5 mmol), 1-benzylpiperazine (88 mg, 0.5 mmol) and sodium triacetoxyborohydride (672 mg, 1.56 mmol) in 10mL CH_2Cl_2 is stirred at RT for 24 h. The mixture is washed with water and dried over anhydrous $MgSO_4$, filtered and the solvent is evaporated to dryness to give 5-[4-(4-benzyl-piperazin-1-ylmethyl)-benzyl]-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one which is used as such in the next step: $[M+1]^+$ = 565.

C. 5-[4-(4-Benzyl-piperazin-1-ylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title B compound, 5-[4-(4-benzyl-piperazin-1-ylmethyl)-benzyl]-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5]thiadiazolidin-3-one (250 mg, 0.44 mmol) dissolved in a mixture of TFA (3mL) and CH_2Cl_2 (3mL) is stirred at RT overnight. The solvent is evaporated and the residue is treated with a mixture of MeCN/water (50/50). The solid is filtered off and the solvent is evaporated to dryness. The residue is treated with cold MeOH (2mL) to afford a white solid which is collected by filtration and washed with Et_2O to afford 5-[4-(4-benzyl-piperazin-1-ylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid: $[M+1]^+$ = 415, $[M-1]^-$ = 413.

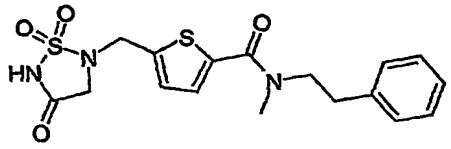
Example 28

The following compounds are prepared by analogously to Example 27.

Example	Chemical Name	MS [m/z]
28-1	1,1-Dioxo-5-{4-[3-oxo-3H-benzofuran-(2Z)-ylidenemethyl]-benzyl}-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 369
28-2	[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetic acid	$[M-1]^-$ = 283
28-3	5-(4-Benzoyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 329
28-4	1-Phenyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-ethane-1,2-dione	$[M-1]^-$ = 357
28-5	5-Naphthalen-2-ylmethyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 275
28-6	5-[4-(4-Methyl-pentanoyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 323
28-7	2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-anthraquinone	$[M-1]^-$ = 355
28-8	5-[3-(2-Fluoro-phenoxy)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 335
28-9	3-{2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-ethoxy}-benzoic acid	$[M-1]^-$ = 389
28-10	1-(3-Methyl-butyl)-6-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-1H-quinolin-2-one	$[M-1]^-$ = 362

Example 29

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid methyl-phenethyl-amide



A. 5-Methyl-thiophene-2-carboxylic acid 2-trimethylsilanyl-ethyl ester

A solution of 5-Methyl-thiophene-2-carboxylic acid (23.58 g, 166 mmol) in MeCN (300 mL) is treated with EDCI (33.41 g, 174 mmol) and DMAP (2.03 g, 16 mmol). The mixture is stirred for 5 min and 2-(trimethylsilyl)ethanol (19.61 g, 166 mmol) is added. The mixture is stirred at RT for 16 h and the solvent is evaporated. The residue is partitioned between EtOAc and water. The organic layer is diluted with an equal portion of hexane and dried over anhydrous $MgSO_4$. The solution is passed through a plug of silica gel and the solvents are evaporated to dryness to give 5-methyl-thiophene-2-carboxylic acid 2-trimethylsilanyl-ethyl ester as a clear oil.

B. 5-Bromomethyl-thiophene-2-carboxylic acid 2-trimethylsilanyl-ethyl ester

A solution of the title A compound, 5-methyl-thiophene-2-carboxylic acid 2-trimethylsilanyl-ethyl ester (34.15 g, 141 mmol) in CCl_4 (200 mL) is treated with N-bromosuccinimide (NBS, 25.08 g, 141 mmol) and 2,2'-azobisisobutyronitrile (1.0 g, 6 mmol). The mixture is irradiated with a 450W mercury lamp for 3 h. An additional 2.5 g of NBS is added and the mixture is further irradiated for 2 h. The mixture is filtered through Celite and a plug of silica gel. The solvent is evaporated to give 5-bromomethyl-thiophene-2-carboxylic acid 2-trimethylsilanyl-ethyl ester as a yellow liquid.

C. 5-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5]thiadiazolidin-2-ylmethyl]-thiophene-2-carboxylic acid 2-trimethylsilanyl-ethyl ester

A solution of the title B compound in Example 9, 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (7.00 g, 24.4 mmol) and DBU (3.71 g, 24.4 mmol) in CH_2Cl_2 (200 mL) is treated with the title B compound, 5-bromomethyl-thiophene-2-carboxylic acid 2-trimethylsilanyl-ethyl ester (8.25 g, 25.7 mmol). The mixture is stirred at RT for 3 h and the solvent is evaporated. The residue is chromatographed over silica gel using 20% - 50% EtOAc in hexane as the eluent to afford 5-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5]thiadiazolidin-2-ylmethyl]-thiophene-2-carboxylic acid 2-trimethylsilanyl-ethyl ester as a yellow oil.

D. 5-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-thiophene-2-carboxylic acid

A solution of the title C compound, 5-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5]thiadiazolidin-2-ylmethyl]-thiophene-2-carboxylic acid 2-trimethylsilanyl-ethyl ester (1.07 g, 2.03 mmol) in anhydrous THF (20 mL) is treated with a 1M solution of tetrabutylammonium fluoride (4.4 mL, 4.46 mmol) in THF at RT for 3 h. The solvent is evaporated and the residue is partitioned between EtOAc and water. The organic layer is washed with 1N aqueous HCl (2X) and dried over anhydrous $MgSO_4$. The solvent is evaporated to afford 5-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-thiophene-2-carboxylic acid as a yellow solid: $[M-1]^-$ = 425.

E. 5-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-thiophene-2-carboxylic acid methyl-phenethyl-amide

A solution of the title D compound, 5-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-thiophene-2-carboxylic acid (220 mg, 0.52 mmol) in toluene (10 mL) is treated with $SOCl_2$ (3 mL) and the mixture is heated at 80°C for 1 h. The volatiles are evaporated and the residue is dissolved in toluene. The solvent is evaporated again and the residue is dissolved in CH_2Cl_2 (10 mL). A mixture of N-methylphenethylamine (35 mg, 0.25 mmol) and triethylamine (39 mg, 38.7 mmol) in CH_2Cl_2 (1 mL) is added and the mixture is stirred for 16 h. The solvent is evaporated and the residue is chromatographed over silica gel using 0-100% EtOAc in hexane as the eluent to afford 5-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-thiophene-2-carboxylic acid methyl-phenethyl-amide as a clear oil: $[M+1]^+$ = 544.

F. 5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid methyl-phenethylamide

A solution of the title E compound, 5-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-thiophene-2-carboxylic acid methyl-phenethyl-amide (70 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) is stirred with TFA (2 mL) at RT for 4 h. The volatiles are evaporated and the residue is stirred in equal volumes of MeCN/ water (4 mL). The mixture is filtered through a 0.2 μ Acrodisc and the solvents are evaporated to dryness. The residue is trituated from Et_2O to afford 5-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid methyl-phenethylamide as an off white solid: $[M-1]^-$ = 392.

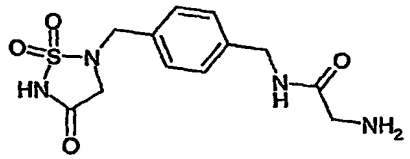
Example 30

The following compounds are prepared analogously to Example 29.

Example	Chemical Name	MS [m/z]
30-1	5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid (2-thiophen-2-yl-ethyl)-amide	$[M-1]^-$ = 384
30-2	5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid phenethyl-amide	$[M-1]^-$ = 378
30-3	[4-(2-{[5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carbonyl]-amino}-ethyl)-phenyl]-acetic acid	$[M-1]^-$ = 436
30-4	5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid 4-carboxy-benzyl ester	$[M-1]^-$ = 409
30-5	5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid isobutyl ester	$[M-1]^-$ = 331
30-6	5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid isobutyl-amide	$[M-1]^-$ = 330

Example 31

2-Amino-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide



A. {4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzyl}-carbamic acid tert-butyl ester

A solution of the title B compound in Example 9, 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (742 mg, 2.59 mmol) and (4-hydroxymethyl-benzyl)-carbamic acid tert-butyl ester (738 mg, 3.11 mmol) in THF (15 mL) is treated with triphenylphosphine (1.36 g, 5.18 mmol). The mixture is stirred for 10 min and diethyl azodicarboxylate (902 mg, 5.18 mmol) is added dropwise over 1 min. The mixture is stirred for 72 h. The solvent is evaporated and the residue is chromatographed on silica gel using 1% MeOH/ CH_2Cl_2 as the eluent to afford {4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzyl}-carbamic acid tert-butyl ester as a white solid: $[M+ NH_4]^+$ = 523.

B. 5-(4-Aminomethyl-benzyl)-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one hydrochloride

The title A compound, {4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzyl}-carbamic acid tert-butyl ester (400 mg, 0.79 mmol) is dissolved in EtOAc (20 mL) with gentle warming. The cooled solution is saturated with HCl gas and stirred for 30 min. The resulting precipitate is collected by filtration, washed with EtOAc and dried to give 5-(4-aminomethyl-benzyl)-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one hydrochloride: $[M+1]^+ = 406$.

C. ({4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzylcarbamoyl}-methyl)-carbamic acid tert-butyl ester

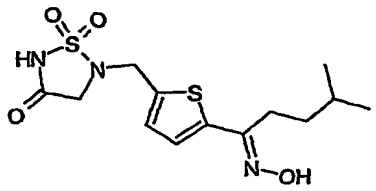
The title B compound, 5-(4-aminomethyl-benzyl)-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one hydrochloride (89 mg, 0.20 mmol) is suspended in dry THF (10 mL) and N-Boc glycine (42 mg, 0.24 mmol) is added. EDCI (58 mg, 0.30 mmol) is added, followed by TEA (61 mg, 0.60 mmol). The mixture is stirred at RT for 16 h. The solvent is evaporated and the residue is chromatographed on silica gel using CH_2Cl_2 → 3% MeOH in CH_2Cl_2 as the eluent to afford ({4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzylcarbamoyl}-methyl)-carbamic acid tert-butyl ester as a white solid: $[M+NH_4]^+ = 580$.

D. 2-Amino-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide

The title C compound, ({4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzylcarbamoyl}-methyl)-carbamic acid tert-butyl ester (80 mg, 0.14 mmol) is stirred in equal volumes of CH_2Cl_2 and TFA (4 mL) for 16 h. The volatiles are evaporated and the residue is stirred in equal volumes of MeCN/ water (5 mL) for 30 min. The mixture is filtered through a 0.2 μ Acrodisc and the solvents are evaporated. The solid is washed with Et_2O and dried to afford 2-amino-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide as a white solid: $[M-1]^- = 311$.

Example 32

5-(5-{1-[(E)-Hydroxyimino]-4-methyl-pentyl}-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one



A. 5-(5-Diethoxymethyl-thiophen-2-ylmethyl)-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title B compound in Example 9, 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (13.9 g, 48.5 mmol), (5-diethoxymethyl-thiophen-2-yl)-methanol (10.5 g, 48.5 mmol) and triphenylphosphine (19.1 g, 72.2 mmol) are dissolved in dry THF (300 mL) and the mixture is cooled to 0°C. Diethyl azodicarboxylate (12.g, 72.7 mmol) is added dropwise over 3 min and the mixture is stirred at RT for 16 h. The solvent is evaporated and the residue is taken up in Et_2O (100 mL). The solution is cooled to 0°C and the precipitate is filtered and discarded. The filtrate is concentrated to dryness and the residue is chromatographed on silica gel using 0 → 100% EtOAc in hexane as the eluent to afford 5-(5-diethoxymethyl-thiophen-2-ylmethyl)-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as an orange oil.

B. 5-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-thiophene-2-carbaldehyde

The title A compound, 5-(5-diethoxymethyl-thiophen-2-ylmethyl)-2-(2,4-dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (3.91 g, 8.1 mmol) is dissolved in THF (100 mL) and 6N aqueous HCl (2.7 mL) is added. The mixture is stirred for 2 h and the solvent is evaporated. The residue is partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The organic layer is dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue is triturated from Et_2O to afford 5-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-thiophene-2-carbaldehyde as a yellow solid.

C. 2-(2,4-Dimethoxy-benzyl)-5-[5-(1-hydroxy-4-methyl-pentyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

A solution of the title B compound, 5-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-thiophene-2-carbaldehyde (545 mg, 1.33 mmol) in dry THF (8 mL) is added dropwise to a cold (-70°C) solution of isopentylmagnesium bromide (2.22 mmol) in dry THF (10 mL) keeping the temperature below –65°C. The mixture is stirred at –70°C for 45 min and the reaction is quenched with saturated aqueous NH_4Cl solution. The mixture is diluted with EtOAc and the layers are separated. The organic layer is dried over anhydrous $MgSO_4$ and the solvent is evaporated. The residue is chromatographed on silica gel using 0 → 100% EtOAc in hexane as the eluent to afford 2-(2,4-dimethoxy-benzyl)-5-[5-(1-hydroxy-4-methyl-pentyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one a yellow oil: $[M+ NH_4]^+$= 500.

D. 2-(2,4-Dimethoxy-benzyl)-5-[5-(4-methyl-pentanoyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title C compound, 2-(2,4-dimethoxy-benzyl)-5-[5-(1-hydroxy-4-methyl-pentyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (125 mg, 0.26 mmol) is dissolved in THF (10 mL) and 4-methylmorpholine N-oxide (152 mg, 1.3 mmol) is added. Tetrapropylammonium perruthenate (TPAP, 9 mg, 0.026 mmol) is added and the mixture is stirred at RT for 1 h. The mixture is filtered through Celite and diluted with EtOAc. The solution is washed with 1N aqueous HCl and the organic layer is dried over anhydrous $MgSO_4$. The solvent is evaporated to afford 2-(2,4-dimethoxy-benzyl)-5-[5-(4-methyl-pentanoyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a clear oil.

E. 2-(2,4-Dimethoxy-benzyl)-5-(5-{1-[-hydroxyimino]-4-methyl-pentyl}-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

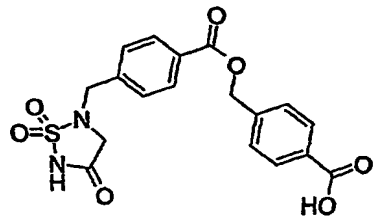
The title D compound, 2-(2,4-dimethoxy-benzyl)-5-[5-(4-methyl-pentanoyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (50 mg, 0.10 mmol) is dissolved in EtOH (5 mL) and water (1 mL) is added. Hydroxylamine hydrochloride (72 mg, 1.0 mmol) is added and the mixture is heated at reflux for 4 h. The solvent is evaporated and the residue is partitioned between EtOAc and water. The organic layer is dried over anhydrous $MgSO_4$ and concentrated to dryness to afford 2-(2,4-dimethoxy-benzyl)-5-(5-{1-[-hydroxyimino]-4-methyl-pentyl}-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a clear oil: $[M+1]^+ = 496$.

F. 5-(5-{1-[(E)-Hydroxyimino]-4-methyl-pentyl}-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title E compound, 2-(2,4-dimethoxy-benzyl)-5-(5-{1-[-hydroxyimino]-4-methyl-pentyl}-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (40 mg, 0.08 mmol) is stirred in equal volumes of CH_2Cl_2 and TFA (4 mL) at RT for 3 h. The volatiles are evaporated and the residue is stirred in equal volumes of MeCN/water (5 mL) for 15 min. The mixture is filtered through a 0.2 μ Acrodisc and the solvents are evaporated to dryness. The residue is triturated from hexane/Et_2O (4:1) to afford 5-(5-{1-[(E)-hydroxyimino]-4-methyl-pentyl}-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a light pink solid: $[M+1]^+ = 346$.

Example 33

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxy-benzyl ester



A. 4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid benzyl ester

The title B compound in Example 9, 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (2.0 g, 7.0 mmol) and 4-hydroxymethyl-benzoic acid benzyl ester (2.54 g, 10.5 mmol) are dissolved in THF (50 mL) in a 200 mL round bottomed flask under nitrogen bubbler. Triphenylphosphine (3.67 g, 14 mmol) is added and stirred until dissolved. The flask is cooled in an ice bath, then diethylazodicarboxylate (2.20 mL, 14 mmol) dissolved in THF (20 mL) is added dropwise. The reaction is allowed to stir 16 h, while letting the ice bath warm to RT. The reaction mixture is concentrated on a rotary evaporator, taken up into CH_2Cl_2, and split into two. Each of these portions is chromatographed on a 110 g silica gel RediSep column (Isco, Inc.) with a 30 mL/min gradient elution of 0:100 (EtOAc:hexane) to 5:95 over 10 min. Fractions containing product are combined and concentrated to yield 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid benzyl ester as a white solid.

B. 4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid

The title A compound, 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid benzyl ester (2.04 g, 4.0 mmol) is suspended in EtOAc/EtOH (1:1, 100 mL) along with 10% palladium on carbon (300 mg) and treated with hydrogen (48 psi) for 4 h on a Parr Shaker. The reaction mixture is filtered through celite and concentrated to give a white solid which is recrystallized from MeOH to yield 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid: $[M-1]^-$ = 419.

C. 4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-tert-butoxycarbonyl-benzyl ester

The title B compound, 4-[5-(2,4-dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid (84 mg, 0.2 mmol) and 4-hydroxymethyl-benzoic acid tert-butyl ester (42 mg, 0.2 mmol) are dissolved in CH_2Cl_2 (3 mL). DMAP (12 mg, 0.1 mmol) is added and the reaction is stirred with cooling to 5°C in an ice bath. EDCI (39 mg, 0.2 mmol) is then added and the reaction is stirred for 16 h. The reaction is concentrated and partioned

between EtOAc and 1N aqueous HCl. The organic solution is washed with saturated aqueous $NaHCO_3$, then saturated aqueous NaCl, then dried over anhydrous $MgSO_4$, filtered and evaporated to give 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-tert-butoxycarbonyl-benzyl ester as a white solid.

D. 4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxy-benzyl ester

The title C compound, 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-tert-butoxycarbonyl-benzyl ester (119 mg, 0.19 mmol) is dissolved in CH_2Cl_2 (5 mL) and then added TFA (5 mL, 64.9 mmol). This is stirred for 2 h and then concentrated under reduced pressure. The residue is suspended in MeCN:water (6:4) (12 mL), centrifuged, decanted and filtered through a 0.1 micron Acrodisc filter. The resulting mixture is loaded onto a preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D., particle size S-5 micron, 12 nM) in 6 aliquots and eluted at 30 mL/min with a gradient of 90:10 (water containing 0.1% TFA: MeCN) at 0 min to 10:90 at 5 min. Then held at 10:90 until 7 min. Fractions containing product are combined and concentrated by lyophilization to yield 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxy-benzyl ester as a white amorphous solid: $[M-1]^-$ = 403.

Example 34

The following compounds are prepared using appropriate starting materials and general methods described in Examples 31, 32 and 33.

Example	Chemical Name	MS [m/z]
34-1	1,1-Dioxo-5-(3-phenoxy-benzyl)-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 317
34-2	3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid	$[M-1]^-$ = 314
34-3	5-(4-Hydroxymethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 255
34-4	2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester	(mp = 181-183°C)
34-5	5-(4-1ydroxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 241
34-6	5-Nitro-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid	$[M-1]^-$ = 314
34-7	5-Amino-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid	$[M-1]^-$ = 284

Example	Chemical Name	MS [m/z]
34-8	5-(4-Chloro-3-methoxy-5-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 334
34-9	5-(2-Nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 270
34-10	5-(3-Methyl-2-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 284
34-11	5-(3-Methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ 239
34-12	1,1-Dioxo-5-(3-phenyl-propyl)-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 253
34-13	5-(4-Butoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 297
34-14	1,1-Dioxo-5-(2-trifluoromethyl-benzyl)-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 293
34-15	3-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid	$[M-1]^-$ = 284
34-16	4-[5-Amino-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-butyric acid	$[M-1]^-$ = 326
34-17	5-(2-Methyl-3-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 284
34-18	5-(4-Methyl-3-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 284
34-19	5-(5-Methyl-2-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 284
34-20	5-(2-Amino-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 240
34-21	2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-isoindole-1,3-dione	$[M-1]^-$ = 384
34-22	2-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-isoindole-1,3-dione	$[M-1]^-$ = 384
34-23	5,5'-[1,4-phenylenebis(methylene)bis[1,2,5-Thiadiazolidine-3-one], 1,1-dioxide	$[M-1]^-$ = 373
34-24	N-[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-oxalamic acid	$[M-1]^-$ = 312
34-25	5-(3-1ydroxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 241
34-26	2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid	$[M-1]^-$ = 284
34-27	5-[5-(4-Nitro-phenyl)-furan-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 336
34-28	5-(4-Fluoro-2-trifluoromethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 311
34-29	5-(3-Hydroxymethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 255
34-30	5-(3-Amino-5-hydroxymethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 270

Example	Chemical Name	MS [m/z]
34-31	5-(3-Amino-4-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M+H]^+ = 256$
34-32	5-(2-Amino-3-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M+H]^+ = 256$
34-33	5-(3-Amino-2-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^- = 254$
34-34	5-(2-Amino-5-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M+H]^+ = 256$
34-35	2,2,2-Trifluoro-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide	$[M-1]^- = 350$
34-36	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-pyridine-2-carbonitrile	$[M-1]^- = 251$
34-37	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-pyridine-2-carboxylic acid ethyl ester	$[M-1]^- = 298$
34-38	5-(3,4-Dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^- = 285$
34-39	5-(3-Amino-5-hydroxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^- = 256$
34-40	5-(3,5-Dimethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^- = 253$
34-41	(S)-3-Phenyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-propionic acid ethyl ester	$[M+H]^+ = 432$
34-42	(S)-3-Phenyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-propionic acid ethyl ester	$[M-1]^- = 430$
34-43	2-Amino-5-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester	$[M-1]^- = 298$
34-44	2-Acetylamino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester	$[M-1]^- = 340$
34-45	5-(2-Benzyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^- = 315$
34-46	5-(2,4-Bis-trifluoromethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^- = 361$
34-47	1,1-Dioxo-5-(2,4,6-trifluoro-benzyl)-1,2,5-thiadiazolidin-3-one	$[M-1]^- = 279$
34-48	5-(2-Bromo-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^- = 303$
34-49	5,5'-[[1,1'-biphenyl]-2,2'-diyl]bis(methylene)bis[1,2,5-Thiadiazolidine-3-one], 1,1-dioxide	$[M-1]^- = 449$
34-50	5-(4-Ethylaminomethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M+H]^+ = 284$
34-51	2-Acetylamino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid	$[M-1]^- = 326$
34-52	2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid ethyl ester	$[M-1]^- = 312$
34-53	1,1-Dioxo-5-[4-(phenethylamino-methyl)-benzyl]-1,2,5-thiadiazolidin-3-one	$[M+H]^+ = 360$

Example	Chemical Name	MS [m/z]
34-54	5-(4-Diethylaminomethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M+H]^+ = 312$
34-55	2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid benzyl ester	$[M-1]^- = 374$
34-56	N-Benzyl-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide	$[M-1]^- = 358$
34-57	5-(5-Dimethylaminomethyl-furan-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M+H]^+ = 274$
34-58	N-[2-(3-Trifluoromethyl-phenyl)-ethyl]-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide	$[M-1]^- = 440$
34-59	N-(3-Methyl-butyl)-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide	$[M+CH_4CN^+]^+ = 381$
34-60	(S)-3-Phenyl-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-propionic acid	$[M-1]^- = 283$
34-61	(R)-3-Phenyl-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-propionic acid	$[M-1]^- = 283$
34-62	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid benzyl ester	$[M-1]^- = 359$
34-63	[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid	$[M-1]^- = 299$
34-64	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid isobutyl ester	$[M-1]^- = 325$
34-65	2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid isobutyl ester	$[M-1]^- = 340$
34-66	[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid methyl ester	$[M-1]^- = 313$
34-67	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxymethoxy-benzyl ester	$[M-1]^- = 433$
34-68	5-(5-Aminomethyl-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^- = 260$
34-69	4-{2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-ethyl}-benzoic acid	$[M+H]^+ = 404$
34-70	[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid isobutyl ester	$[M-1]^- = 355$
34-71	[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid benzyl ester	$[M-1]^- = 389$
34-72	N-Isobutyl-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide	$[M-1]^- = 324$

Example	Chemical Name	MS [m/z]
34-73	5-(5-Diethylaminomethyl-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	[M+H]$^+$ = 318
34-74	4-(2-{[5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophen-2-ylmethyl]-amino}-ethyl)-benzoic acid	[M+H]$^+$ = 410
34-75	3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester	[M-1]$^-$ = 328
34-76	3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid ethyl ester	[M-1]$^-$ = 342
34-77	3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid isobutyl ester	[M-1]$^-$ = 370
34-78	5-(4-Ethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one	[M-1]$^-$ = 269
34-79	1,1-Dioxo-5-(3-trifluoromethyl-benzyl)-1,2,5-thiadiazolidin-3-one	[M-1]$^-$ = 293
34-80	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxymethyl-benzyl ester	[M-1]$^-$ = 417
34-81	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid phenethyl ester	[M-1]$^-$ = 373
34-82	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-phenylamino-ethyl ester	[M-1]$^-$ = 388
34-83	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-(3-methoxy-phenyl)-ethyl ester	[M-1]$^-$ = 403
34-84	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl ester	[M-1]$^-$ = 507
34-85	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2,2-dimethyl-propyl ester	[M-1]$^-$ = 339
34-86	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methoxycarbonyl-2-methyl-propyl ester	[M-1]$^-$ = 383
34-87	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2,2,4-trimethyl-pentyl ester	[M-1]$^-$ = 381
34-88	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-dimethylamino-2,2-dimethyl-propyl ester	[M-1]$^-$ = 382
34-89	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid (3aR,4S,5R,6aS)-5-benzoyloxy-2-oxo-hexahydro-cyclopenta[b]furan-4-ylmethyl este r	[M-1]$^-$ = 527
34-90	6-{[5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophen-2-ylmethyl]-amino}-hexanoic acid	[M+H]$^+$ = 376
34-91	5-{5-[(3-Methyl-butylamino)-methyl]-thiophen-2-ylmethyl}-1,1-dioxo-1,2,5-thiadiazolidin-3-one	[M+H]$^+$ = 332
34-92	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-methyl-4-nitro-benzyl ester	[M-1]$^-$ = 418

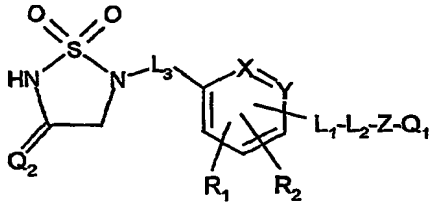
Example	Chemical Name	MS [m/z]
34-93	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-chloro-4-methyl-benzyl ester	$[M-1]^-$ = 407
34-94	5-[5-(Isobutylamino-methyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M+H]^+$ = 318
34-95	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-ethoxycarbonyl-pentyl ester	$[M-1]^-$ = 411
34-96	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-(3-chloro-phenyl)-ethyl ester	$[M-1]^-$ = 407
34-97	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-m-tolyl-ethyl ester	$[M-1]^-$ = 387
34-98	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-(3-trifluoromethyl-phenyl)-ethyl ester	$[M-1]^-$ = 441
34-99	(R)-3-Phenyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-propionic acid ethyl ester	$[M-1]^-$ = 430
34-100	5-[4-(Benzylamino-methyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 344
34-101	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methyl-benzyl ester	$[M-1]^-$ = 373
34-102	4-Methyl-6-{[5-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophen-2-ylmethyl]-amino}-hexanoic acid	$[M-1]^-$ = 388
34-103	4-[(1,1,4-trioxido-1,2,5-thiadiazolidin-2-yl)methyl]-benzoic acid [4-(methoxycarbonyl)phenyl]methyl ester	$[M-1]^-$ = 417
34-104	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-cyclohexyl-2-methyl-propyl ester	$[M-1]^-$ = 407
34-105	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-phenoxy-propyl ester	$[M-1]^-$ = 403
34-106	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-trifluoromethyl-benzyl ester	$[M-1]^-$ = 427
34-107	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-trifluoromethyl-benzyl ester	$[M-1]^-$ = 427
34-108	4-[(1,1,4-trioxido-1,2,5-thiadiazolidin-2-yl)methyl]-benzoic acid 2-(4-carboxyphenyl)ethyl ester	$[M-1]^-$ = 417
34-109	5-[5-(3-Methyl-butyryl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 315
34-110	3-[[[4-[(1,1,4-Trioxido-1,2,5-thiadiazolidin-2-yl)methyl]benzoyl]-oxy]methyl]benzoic acid	$[M-1]^-$ = 403
34-111	5-[4-(Isobutylamino-methyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 310

Example	Chemical Name	MS [m/z]
34-112	5-{4-[(2,2-Dimethyl-propylamino)-methyl]-benzyl}-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 324
34-113	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid naphthalen-1-ylmethyl ester	$[M-1]^-$ = 409
34-114	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-nitro-benzyl ester	$[M-1]^-$ = 404
34-115	(4-{2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoylamino]-ethyl}-phenyl)-acetic acid	$[M+H]^+$ = 432
34-116	5-[5-(4-Methyl-pentanoyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 329
34-117	5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid	$[M-1]^-$ = 275
34-118	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-nitro-benzyl ester	$[M-1]^-$ = 404
34-119	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-(carboxymethyl-amino)-2,2-dimethyl-propyl ester	$[M-1]^-$ = 412
34-120	5-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyloxymethyl]-thiophene-2-carboxylic acid	$[M-1]^-$ = 409
34-121	5-[4-(4-Benzyl-piperazin-1-ylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 413
34-122	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid biphenyl-4-ylmethyl ester	$[M-1]^-$ = 435
34-123	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-acetylamino-benzyl ester	$[M-1]^-$ = 416
34-124	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-benzyl-benzyl ester	$[M-1]^-$ = 449
34-125	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methyl-benzyl ester	$[M-1]^-$ = 373
34-126	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methyl-3-nitro-benzyl ester	$[M-1]^-$ = 418
34-127	Glycine, N-(aminosulfonyl)-N-[[4-[[(2-phenylethyl)thio]methyl]phenyl]methyl]-, methyl ester	$[M-1]^-$ = 407
34-128	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-carboxymethyl-benzyl ester	$[M-1]^-$ = 417
34-129	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methyl-3-nitro-benzyl ester	$[M-1]^-$ = 418
34-130	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-fluoro-2-trifluoromethyl-benzyl ester	$[M-1]^-$ = 445

Example	Chemical Name	MS [m/z]
34-131	4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-benzyl ester	$[M-1]^-$ = 643
34-132	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-benzyl ester	$[M-1]^-$ = 493
34-133	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-methyl-2-nitro-benzyl ester	$[M-1]^-$ = 418
34-134	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid o-tolyl ester	$[M-1]^-$ = 359
34-135	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-(carboxymethyl-methyl-amino)-2,2-dimethyl-propyl ester	$[M-1]^-$ = 426
34-136	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid phenyl ester	$[M-1]^-$ = 345
34-137	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-isobutylcarbamoyl-thiophen-2-ylmethyl ester	$[M-1]^-$ = 464
34-138	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid naphthalen-2-ylmethyl ester	$[M-1]^-$ = 409
34-139	N,N-Diisobutyl-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide	$[M+H]^+$ = 382
34-140	{4-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-piperazin-1-yl}-acetic acid	$[M+H]^+$ = 397
34-141	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid naphthalen-2-yl ester	$[M-1]^-$ = 395
34-142	5-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyloxymethyl]-thiophene-2-carboxylic acid isobutyl ester	$[M-1]^-$ = 465
34-143	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-carbamoyl-thiophen-2-ylmethyl ester	$[M-1]^-$ = 408
34-144	5-[4-(4-Benzyl-piperazine-1-carbonyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one	$[M-1]^-$ = 427
34-145	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-(3-phenyl-propionyl)-thiophen-2-ylmethyl ester	$[M-1]^-$ = 497
34-146	4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-benzylcarbamoyl-thiophen-2-ylmethyl ester	$[M-1]^-$ = 498

What is claimed is:

1. A compound of the formula



(I)

wherein

R_1 and R_2 are independently hydrogen, halogen, hydroxy, alkoxy, carboxy, cyano, nitro, trifluoromethyl, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, alkylthio, aralkylthio, arylthio, optionally substituted amino, aralkyl, aralkoxy, aryloxy, heteroaralkyl, heteroaralkoxy or heteroaryloxy; or

C-R_1 is nitrogen or N→O; or

R_1 and R_2 combined together with the carbon atoms to which R_1 and R_2 are attached form an optionally substituted fused 5- to 6-membered aromatic or heteroaromatic ring provided that R_1 and R_2 are attached to carbon atoms adjacent to each other; or

R_2 is $-C(O)R_3$ wherein

R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

L_1 is a single bond; or

L_1 is carbon which combined together with R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is CH or nitrogen which taken together with R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur; or

L_1 is CH, oxygen, sulfur or nitrogen provided L_2 is carbon which combined together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is $-CH_2-$, oxygen, sulfur or $-NR_6-$ provided L_2 is CH which taken together with L_1,

R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl; or

L_2 is $-(CHR_7)_n-$ wherein

R_7 is hydrogen, hydroxy, alkoxy, carboxy, optionally substituted alkyl, cycloalkyl, aryl or heteroaryl;

n is zero or an integer from 1 to 4;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, carbamoyl, sulfonyl, acyl or acylamino;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(a) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl provided that Q_1 is not hydrogen when

R_1 and R_2 are hydrogen;

X and Y are CH;

L_1 is a single bond;

L_2 is $-(CHR_7)_n-$ wherein R_7 is hydrogen and n is zero;

Z is $-(CHR_8)_m-$ wherein R_8 is hydrogen and m is zero;

L_3 is $-(CHR_7)_s-$ wherein R_8 is hydrogen and s is 1; and

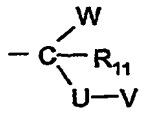
Q_2 is oxygen

(b) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are as defined for R_3;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

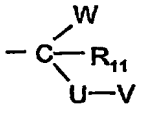
U is $-C(O)-$, $-S(O)_2-$ or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

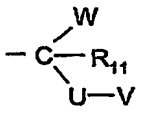
R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero; or

(e) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl,

aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is $-NR_4R_5$, and R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

L_3 is $-(CHR_7)_s-$ wherein

R_7 is as defined for L_2;

s is an integer from 1 to 3;

Q_2 is oxygen, sulfur or NR_{13} wherein

R_{13} is hydrogen, hydroxy or lower alkyl;

X and Y are independently CH or nitrogen; or

$-X=Y-$ is sulfur, oxygen or $-NR_{14}-$ wherein

R_{14} is hydrogen, optionally substituted alkyl, alkoxycarbonyl, acyl, aryloxycarbonyl, heteroaryloxycarbonyl, carbamoyl or sulfonyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

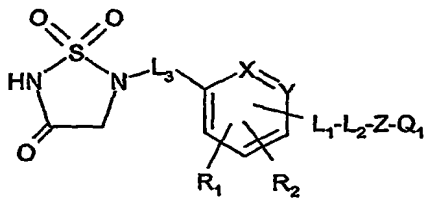
2. A compound according to claim 1 wherein

Q_2 is oxygen;

X and Y are CH; or

$-X=Y-$ is sulfur; or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

3. A compound according to claim 2 of the formula



(IA)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy, aryloxy, heteroaralkyl or heteroaralkoxy;

R_2 is hydrogen; or

R_2 is -C(O)R_3 wherein

R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is -NR_4R_5 in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

L_1 is a single bond; or

L_1 is carbon which combined together with R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is CH or nitrogen which taken together with R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur; or

L_1 is CH, oxygen, sulfur or nitrogen provided L_2 is carbon which combined together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is -CH_2-, oxygen, sulfur or -NR_6- provided L_2 is CH which taken together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl; or

L_2 is -$(CHR_7)_n$- wherein

R_7 is hydrogen;

n is zero or an integer of 1 or 2;

Z is -$(CHR_8)_m$-, -$(CH_2)_mO(CHR_8)_r$-, -$(CH_2)_mS(CHR_8)_r$- or -$(CH_2)_mNR_9(CHR_8)_r$- wherein

R_8 is hydrogen or optionally substituted alkyl;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(a) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl provided that Q_1 is not hydrogen when

R_1 and R_2 are hydrogen;

X and Y are CH;

L_1 is a single bond;

L_2 is $-(CHR_7)_n-$ wherein R_7 is hydrogen and n is zero;

Z is $-(CHR_8)_m-$ wherein R_8 is hydrogen and m is zero; and

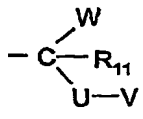
L_3 is $-(CHR_7)_s-$ wherein R_8 is hydrogen and s is 1;

(b) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are as defined for R_3;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

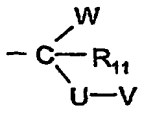
U is -C(O)- or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

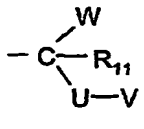
R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero; or

(e) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is $-NR_4R_5$, and R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

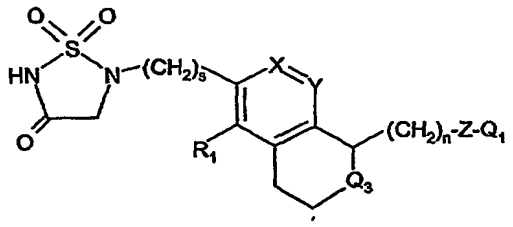
L_3 is $-(CHR_7)_s-$ wherein

R_7 is as defined for L_2;

s is an integer from 1 to 3;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

4. A compound according to claim 3 of the formula



(IB)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio,

aralkyl, aralkoxy, aryloxy, heteroaralkyl or heteroaralkoxy;

n is zero or an integer of 1 or 2;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

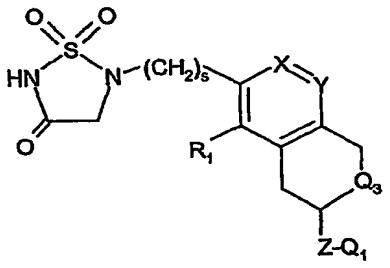
s is an integer of 1 or 2;

Q_3 is O, S or $-NR_6-$ wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

5. A compound according to claim 3 of the formula



(IC)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy, aryloxy, heteroaralkyl or heteroaralkoxy;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

s is an integer of 1 or 2;

Q_3 is O, S or $-NR_6-$ wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

6. A compound according to claim 3 wherein

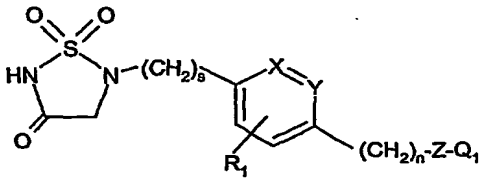
R_2 is hydrogen;

L_1 is a single bond;

L_2 is $-(CH_2)_n-$ in which n is zero or an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

7. A compound according to claim 6 of the formula



(ID)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy or aryloxy;

n is zero or an integer of 1 or 2;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(a) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl provided that Q_1 is not hydrogen when

R_1 is hydrogen;

X and Y are CH;

n is zero;

Z is $-(CHR_8)_m-$ wherein m is zero; and

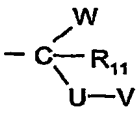
L_3 is $-(CH_2)_s-$ wherein s is 1;

(b) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally

substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

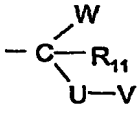
U is -C(O)- or -$(CH_2)_r$- in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is -NR_4R_5 provided that

n is an integer of 1 or 2; and

Z is -$(CHR_8)_m$- in which m is zero;

(d) a radical of the formula  wherein

W is -$C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is -NR_4R_5 in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

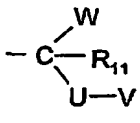
R_{11} is hydrogen, alkyl or aryl;

U is -$(CH_2)_p$- in which p is zero or 1;

V is -$NR_4C(O)R_5$, -$NR_4C(O)OR_5$, -$NR_4C(O)NR_4R_5$ or -$NR_4S(O)_2R_5$ provided that

n is an integer of 1 or 2; and

Z is -$(CHR_8)_m$- in which m is zero; or

(e) a radical of the formula  wherein

W is -$C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is -NR_4R_5 in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

U is -$(CH_2)_r$- in which r is zero or 1;

V is -$NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is

$-NR_4R_5$ provided that

n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

s is 1;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

8. A compound according to claim 7 wherein

-X=Y- is sulfur;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

9. A compound according to claim 7 wherein

R_1 is bromide;

X and Y are CH;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

10. A compound according to claim 7 wherein

n is zero;

Z is $-(CH_2)_m-$ in which m is zero;

Q is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

11. A compound according to claim 7 wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_mO(CH_2)_r-$ or $-(CH_2)_mS(CH_2)_r-$ wherein

m is zero;

r is zero or 1;

Q_1 is optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

12. A compound according to claim 7 wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_mNR_9(CH_2)_r-$ wherein

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl or acyl;

m is zero;

r is zero or 1;

Q_1 is optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

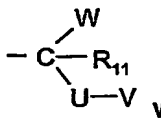
q is an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

13. A compound according to claim 7 wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

U is -C(O)- or $-(CH_2)_r-$ in which r is zero;

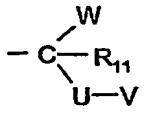
V is aryl, heteroaryl, optionally substituted alkyl or cycloalkyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

14. A compound according to claim 7 wherein

n is 1;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen;

U is $-(CH_2)_p-$ in which p is zero;

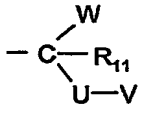
V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

15. A compound according to claim 7 wherein

n is 1;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is $-NR_4R_5$, and R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen;

U is $-(CH_2)_p-$ in which p is zero;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl or alkoxy; or R_{12} is $-NR_4R_5$;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

16. A compound of claim 1 which is selected from a group consisting of:
5-Naphthalen-1-ylmethyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
N-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide;
[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-carbamic acid tert-butyl ester;
5-(4-Aminomethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide;
[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-carbamic acid tert-butyl ester;
3-Phenyl-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-propionamide;
5-(3-Iodo-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
5-(3-Nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
5-(3-Amino-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
N-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide;
1,1-Dioxo-5-pyridin-4-ylmethyl-1,2,5-thiadiazolidin-3-one;
5-(4-Amino-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
N-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-butyramide;
1-Propyl-3-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-urea;
4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester;
4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;
2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;
5-(2-Methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
1,1-Dioxo-5-pyridin-3-ylmethyl-1,2,5-thiadiazolidin-3-one;
1,1-Dioxo-5-pyridin-2-ylmethyl-1,2,5-thiadiazolidin-3-one;
5-(6-Amino-pyridin-3-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
1,1-Dioxo-5-thiophen-2-ylmethyl-1,2,5-thiadiazolidin-3-one;
5-(4-Methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
5-(4-Amino-2-bromo-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide;
N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-methanesulfonamide;
N-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-methanesulfonamide;
5-(4-Methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;
Amino-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetic acid;
2-Amino-N-propyl-2-[2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide;
2-Amino-N-propyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide;

2,2,2-Trifluoro-N-{propylcarbamoyl-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-methyl}-acetamide;

2-Methanesulfonylamino-N-propyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetamide;

2-Acetylamino-N-propyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-propionamide;

2-Acetylamino-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-malonic acid diethyl ester;

2-Amino-N-propyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-propionamide;

2-Acetylamino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-propionic acid ethyl ester;

Phenyl-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-acetic acid;

1,1-Dioxo-5-phenethyl-1,2,5-thiadiazolidin-3-one;

5-[2-(4-Methyl-thiazol-5-yl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-(3,4-Dimethoxy-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-(2-Chloro-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-(4-Amino-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2,2,2-Trifluoro-N-{4-[2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-ethyl]-phenyl}-acetamide;

N-{4-[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-ethyl]-phenyl}-butyramide;

1,1-Dioxo-5-(2-pyridin-3-yl-ethyl)-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(2-pyridin-4-yl-ethyl)-1,2,5-thiadiazolidin-3-one;

3-Phenyl-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-propionic acid;

5-[2-(3-Amino-phenyl)-ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Aminomethyl-naphthalen-1-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(1-Ethyl-2-methyl-1H-benzimidazol-5-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[2-Methyl-1-(3-methyl-butyl)-1H-benzimidazol-5-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Methoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Isobutoxy-quinolin-7-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

{(1-Butylcarbamoyl-3-phenyl-propyl)-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[Butylcarbamoyl-(4-ethyl-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[Butylcarbamoyl-(3-phenoxy-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[Butylcarbamoyl-(4-methoxy-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[(2-Bromo-phenyl)-butylcarbamoyl-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

(Butylcarbamoyl-naphthalen-2-yl-methyl)-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[Butylcarbamoyl-(4-chloro-phenyl)-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{[(3-Benzyloxy-phenyl)-butylcarbamoyl-methyl]-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

{((E)-1-Butylcarbamoyl-3-phenyl-allyl)-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-amino}-acetic acid;

N-(1-Butylcarbamoyl-3-phenyl-propyl)-N-(4-(1,1,4-trioxo-1,2,5-thiazodiazolidin-2-ylmethyl)-benzoyl)-amino-acetic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methanesulfonyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-chloro-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-butyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-hydroxymethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-phenethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid biphenyl-2-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-difluoromethoxy-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-(carboxy-difluoro-methyl)-thiophen-2-ylmethyl ester;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenylmethanesulfonyl]-acetic acid ethyl ester;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylsulfanyl]-acetic acid ethyl ester;

5-[4-(3-Methyl-butylsulfanylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-ethyl-butyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid cyclobutylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid cyclopentylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methyl-pentyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2,4,4-trimethyl-pentyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid cyclohexylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 1,2-dimethyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid cyclopentyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methyl-butyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methylsulfanyl-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-carboxymethylsulfanyl-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-nitro-furan-2-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid pyridin-2-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-hydroxymethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-methanesulfonyl-benzyl ester;

(4-{4-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoylamino]-butyl}-phenyl)-acetic acid;

(4-{3-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoylamino]-propyl}-phenyl)-acetic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-dimethylaminomethyl-furan-2-ylmethyl ester;

(S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-ethyl}-3-phenyl-propionamide;

5-(1H-Indol-5-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(3,4,5-trimethoxy-benzyl)-1,2,5-thiadiazolidin-3-one;

5-[4-(4-Benzyl-piperazin-1-ylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-acetic acid;

5-(4-Benzoyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-Naphthalen-2-ylmethyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[4-(4-Methyl-pentanoyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-[3-(2-Fluoro-phenoxy)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

3-{2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-ethoxy}-benzoic acid;

1-(3-Methyl-butyl)-6-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-1H-quinolin-2-one;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid methyl-phenethyl-amide;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid (2-thiophen-2-yl-ethyl)-amide;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid phenethyl-amide;

[4-(2-{[5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carbonyl]-amino}-ethyl)-phenyl]-acetic acid;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid 4-carboxy-benzyl ester;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid isobutyl ester;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid isobutyl-amide;

2-Amino-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide;

4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxy-benzyl ester;

1,1-Dioxo-5-(3-phenoxy-benzyl)-1,2,5-thiadiazolidin-3-one;

3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

5-(4-1ydroxymethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester;

5-(4-1ydroxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-Nitro-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

5-Amino-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

5-(4-Chloro-3-methoxy-5-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(2-Nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Methyl-2-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(3-phenyl-propyl)-1,2,5-thiadiazolidin-3-one;

5-(4-Butoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(2-trifluoromethyl-benzyl)-1,2,5-thiadiazolidin-3-one;

3-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

4-[5-Amino-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-butyric acid;

5-(2-Methyl-3-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Methyl-3-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(5-Methyl-2-nitro-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(2-Amino-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-isoindole-1,3-dione;

2-[3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-isoindole-1,3-dione;

5,5'-[1,4-phenylenebis(methylene)bis[1,2,5-Thiadiazolidine-3-one], 1,1-dioxide;

N-[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenyl]-oxalamic acid;

5-(3-1ydroxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

5-[5-(4-Nitro-phenyl)-furan-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(4-Fluoro-2-trifluoromethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-1ydroxymethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Amino-5-hydroxymethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Amino-4-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(2-Amino-3-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Amino-2-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(2-Amino-5-methyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2,2,2-Trifluoro-N-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl]-acetamide;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-pyridine-2-carbonitrile;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-pyridine-2-carboxylic acid ethyl ester;

5-(3,4-Dimethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3-Amino-5-hydroxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(3,5-Dimethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

(S)-3-Phenyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-propionic acid ethyl ester;

(S)-3-Phenyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-propionic acid ethyl ester;

2-Amino-5-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester;

2-Acetylamino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester;

5-(2-Benzyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(2,4-Bis-trifluoromethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(2,4,6-trifluoro-benzyl)-1,2,5-thiadiazolidin-3-one;

5-(2-Bromo-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5,5'-[[1,1'-biphenyl]-2,2'-diyl]bis(methylene)bis[1,2,5-Thiadiazolidine-3-one], 1,1-dioxide;

5-(4-Ethylaminomethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2-Acetylamino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid;

2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid ethyl ester;

1,1-Dioxo-5-[4-(phenethylamino-methyl)-benzyl]-1,2,5-thiadiazolidin-3-one;

5-(4-Diethylaminomethyl-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid benzyl ester;

N-Benzyl-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide;

5-(5-Dimethylaminomethyl-furan-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

N-[2-(3-Trifluoromethyl-phenyl)-ethyl]-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide;

N-(3-Methyl-butyl)-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide;

(S)-3-Phenyl-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-propionic acid;

(R)-3-Phenyl-2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-propionic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid benzyl ester;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid isobutyl ester;

2-Amino-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid isobutyl ester;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid methyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxymethoxy-benzyl ester;

5-(5-Aminomethyl-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-{2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-ethyl}-benzoic acid;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid isobutyl ester;

[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-phenoxy]-acetic acid benzyl ester;

N-Isobutyl-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide;

5-(5-Diethylaminomethyl-thiophen-2-ylmethyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(2-{[5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophen-2-ylmethyl]-amino}-ethyl)-benzoic acid;

3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid methyl ester;

3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid ethyl ester;

3-Nitro-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid isobutyl ester;

5-(4-Ethoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

1,1-Dioxo-5-(3-trifluoromethyl-benzyl)-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-carboxymethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid phenethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-phenylamino-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-(3-methoxy-phenyl)-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2,2-dimethyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methoxycarbonyl-2-methyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2,2,4-trimethyl-pentyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-dimethylamino-2,2-dimethyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid (3aR,4S,5R,6aS)-5-benzoyloxy-2-oxo-hexahydro-cyclopenta[b]furan-4-ylmethyl ester;

6-{[5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophen-2-ylmethyl]-amino}-hexanoic acid;

5-{5-[(3-Methyl-butylamino)-methyl]-thiophen-2-ylmethyl}-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-methyl-4-nitro-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-chloro-4-methyl-benzyl ester;

5-[5-(Isobutylamino-methyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-ethoxycarbonyl-pentyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-(3-chloro-phenyl)-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-m-tolyl-ethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-(3-trifluoromethyl-phenyl)-ethyl ester;

(R)-3-Phenyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzylamino]-propionic acid ethyl ester;

5-[4-(Benzylamino-methyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methyl-benzyl ester;

4-Methyl-6-{[5-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophen-2-ylmethyl]-amino}-hexanoic acid;

4-[(1,1,4-trioxido-1,2,5-thiadiazolidin-2-yl)methyl]-benzoic acid [4-(methoxycarbonyl)-phenyl]methyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-cyclohexyl-2-methyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-phenoxy-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-trifluoromethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-trifluoromethyl-benzyl ester;

4-[(1,1,4-trioxido-1,2,5-thiadiazolidin-2-yl)methyl]-benzoic acid 2-(4-carboxyphenyl)ethyl ester;

5-[5-(3-Methyl-butyryl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

3-[[[4-[(1,1,4-Trioxido-1,2,5-thiadiazolidin-2-yl)methyl]benzoyl]-oxy]methyl]benzoic acid;

5-[4-(Isobutylamino-methyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-{4-[(2,2-Dimethyl-propylamino)-methyl]-benzyl}-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid naphthalen-1-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-nitro-benzyl ester;

(4-{2-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoylamino]-ethyl}-phenyl)-acetic acid;

5-[5-(4-Methyl-pentanoyl)-thiophen-2-ylmethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

5-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-thiophene-2-carboxylic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-nitro-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-(carboxymethyl-amino)-2,2-dimethyl-propyl ester;

5-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyloxymethyl]-thiophene-2-carboxylic acid;

5-[4-(4-Benzyl-piperazin-1-ylmethyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid biphenyl-4-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-acetylamino-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-benzyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 2-methyl-3-nitro-benzyl ester;

Glycine, N-(aminosulfonyl)-N-[[4-[[(2-phenylethyl)thio]methyl]phenyl]methyl]-, methyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-carboxymethyl-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-methyl-3-nitro-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-fluoro-2-trifluoromethyl-benzyl ester;

4-[5-(2,4-Dimethoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl]-benzoic acid 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-methyl-2-nitro-benzyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid o-tolyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 3-(carboxymethyl-methyl-amino)-2,2-dimethyl-propyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid phenyl ester

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-isobutylcarbamoyl-thiophen-2-ylmethyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid naphthalen-2-ylmethyl ester;

N,N-Diisobutyl-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzamide;

{4-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyl]-piperazin-1-yl}-acetic acid;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid naphthalen-2-yl ester;

5-[4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoyloxymethyl]-thiophene-2-carboxylic acid isobutyl ester;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-carbamoyl-thiophen-2-ylmethyl ester;

5-[4-(4-Benzyl-piperazine-1-carbonyl)-benzyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-(3-phenyl-propionyl)-thiophen-2-ylmethyl ester; and

4-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-ylmethyl)-benzoic acid 5-benzylcarbamoyl-thiophen-2-ylmethyl ester; or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

17. A method for the inhibition of PTP-1B activity in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

18. A method for the treatment of conditions associated with PTP-1B activity in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

19. The method according to claim 18, which method comprises administering said compound in combination with a therapeutically effective amount of insulin, insulin derivative or mimetic, insulin secretagogue, insulinotropic sulfonylurea receptor ligand, insulin sensitizer, alpha-glucosidase inhibitor, GLP-1, GLP-1 analog or mimetic, DPP-IV inhibitor, hypolipidemic agent, cholestyramine, fibrate, nicotinic acid, anti-hypertensive agent, anti-obesity agent, or aspirin.

20. A method for modulating glucose levels in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

21. A method for the treatment and/or prevention of diabetes in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

22. A method for the treatment and/or prevention of metabolic disorders mediated by insulin resistance in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

23. A method for the treatment and/or prevention of atherosclerosis in mammals which method comprises administering to a mammal in need thereof a therapeutically effective

amount of a compound of claim 1 in combination with a therapeutically effective amount of an HMG-CoA reductase inhibitor.

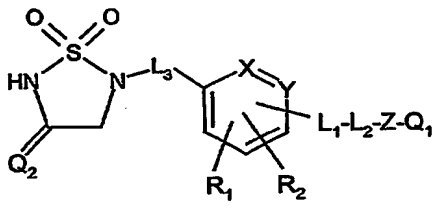
24. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with one or more pharmaceutically acceptable carriers.

25. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a therapeutically effective amount of insulin, insulin derivative or mimetic, insulin secretagogue, insulinotropic sulfonylurea receptor ligand, insulin sensitizer, biguanide, alpha-glucosidase inhibitor, GLP-1, GLP-1 analog or mimetic, DPP-IV inhibitor, hypolipidemic agent, cholestyramine, fibrate, nicotinic acid, anti-hypertensive agent, anti-obesity agent, or aspirin.

CYCLIC SULFAMIDE DERIVATIVES AND METHODS OF USE

ABSTRACT OF THE DISCLOSURE

Compounds of the formula



(I)

provide pharmacological agents which are inhibitors of PTPases, in particular, the compounds of the present invention inhibit PTP-1B, and thus may be employed for the treatment of conditions associated with PTPase activity. The compounds of the present invention may also be employed for inhibition of other enzymes with a phosphotyrosine binding region such as the SH2 domain. Accordingly, the compounds of formula I may be employed for prevention or treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels. The compounds of the present invention may also be employed in the treatment, prevention or control of a number of conditions that accompany Type 2 diabetes, including hyperlipidemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, irritable bowel syndrome, pancreatitis, adipose cell tumors and carcinomas such as liposarcoma, dyslipidemia, and other disorders where insulin resistance is indicated. In addition, the compounds of the present invention may be employed to treat or prevent cancer, osteoporosis, neurodegenerative and infectious diseases, and diseases involving inflammation and the immune system.